The neural   substrates of inferential and referential semantic processing

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The neural substrates of inferential and referential semantic processing

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ABSTRACT

Introduction: A distinction has been proposed, on theoretical grounds, between referential and inferential semantic abilities. The former account for the relationship of words to the world, the latter for the relationship of words among themselves. The hypothesis of, at least partially, different neurological underpinnings for this distinction has been supported by the presence of double dissociations in neurological patients between tasks that can be considered to tap the cognitive processes involving these two different classes of semantic knowledge, such as, for example, picture naming (referential) and naming to a verbal definition (inferential).

Methods: We report here the results of a functional magnetic resonance experiment, contrasting the pattern of brain activity associated with, respectively, "referential" (picture naming, word-to-picture matching) and "inferential" (naming to definition, word-to-word matching) tasks.

Results: All tasks activate an extensive set of brain areas involving both hemispheres, corresponding to the "common semantic network". In addition, left hemispheric temporal areas are selectively engaged by the inferential tasks. Conversely, a specific activation of the right fusiform gyrus is associated with the referential tasks.

Conclusions: These findings suggest that while inferential tasks, as compared with referential tasks, engage additional processing resources subserved by left hemispheric language areas involved in lexical retrieval, referential tasks (as compared with inferential tasks) recruit right hemispheric areas generally associated with nonverbal conceptual and structural object processing. These findings are compatible with the double dissociations reported in neurological patients.

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1. Introduction

Competence on words involves phonological, morphological and syntactic abilities. In addition, it involves abilities that are usually characterized as "semantic". These appear to be of two kinds (Marconi, 1997). On the one hand, we know how to relate words to other words. We know that *cats* are *animals*, we can verbally describe the difference between *walking* and *running*, we understand that "a polished or smooth surface that forms images by reflection" is a *mirror*. On the other hand, we know how to relate words to the world out there, as presented to us in perception. We can tell cats from cows by calling the former *cats* and the latter *cows*, we can describe a man as *running* rather than *walking*, and we can pick up the appropriate tool if requested to obey the order "Bring me the hammer, not the pliers!". The former have been called 'inferential' and the latter 'referential' abilities. Inferential abilities lie at the basis of so-called "material inferences" (cf. Brandom, 1994), such as the inference from 'Felix is a cat' to 'Felix is a mammal' or from 'Milan is north of Rome' to 'Rome is south of Milan' (as distinct from *logical* inferences, such as the inference from 'If it's Thursday I have a class' and 'It's Thursday' to 'I have a class'). Referential abilities, in turn, cognitively mediate the relation of reference between words and things. The distinction between inferential and referential abilities should not be conflated with the distinction between inferential role semantics and referential (or truth conditional) semantics, familiar from the philosophy of mind and language (see Block, 1986). The latter is a distinction between different theoretical accounts of meaning, whereas the former concerns (lexical) semantic competence. While truth conditional semantics aims at determining objective truth conditions that may elude the abilities of every speaker in a linguistic community (Putnam, 1975), referential competence coincides with the ability a speaker has to relate words to the world thanks to perception and other cognitive faculties.

Relative to many ordinary words, most of us are quite competent both inferentially and referentially. However, for many other words competence varies widely from speaker to speaker. For example, a trained zoologist may be more competent than most of us on the word *manatee* (as she is more competent on manatees, the animals themselves). Moreover, an individual speaker may be more competent referentially than inferentially: a person may be extremely skilled at telling primroses from other flowers without knowing the first things about primroses, while a bookish scientist may know all there is to know about a rare tropical flower while having trouble to recognize one, as she never saw it in nature. Thus, the two sides of lexical semantic competence can be said to be relatively independent of each other (see Marconi, 1997 for further details).

In principle, there is no reason to expect that distinct abilities underlie the intuitive distinction between inferential and referential performances, or that they are implemented by distinct functional subsystems in the brain. The distinction might only be a classification of patterns of behavior involved in ordinary use of the lexicon. Some evidence from both neuropsychological case studies and (to a lesser extent) neuroimaging, however, seems to indicate that the distinction

might be neurally implemented, i.e., that different subsystems with partly distinct neural realizations might be responsible for cognitive performances involving inferential and referential aspects of semantics, respectively. It is evident that, from the point of view of the access to information, referential semantics has a close connection to perceptual modalities, in particular to vision, but also to audition and somatosensory perception. An impairment in referential tasks may thus reflect defective access of perceptual information to the semantic system, as in the case of the classical "disconnection syndromes" (for a recent review see Catani and ffytche, 2005), while an apparent inferential impairment may be the consequence of a language disorder.

How could the distinction between referential and inferential performances be mapped on the tasks that have been used in neuropsychology? In clinical neuropsychology, a distinction is traditionally made between *naming* tasks (including production of a noun corresponding to a picture, or to a linguistic definition) and *matching* tasks (including selection of a picture or a word matching a word stimulus among alternatives), assessing, respectively, language production and comprehension at the single word level. From the point of view of the cognitive processes involved, all these tasks share the requirements for visual perceptual analysis, access to lexical and semantic information and lexical retrieval. According to the previous distinction (Marconi, 1997), however, picture naming and word-to-picture matching can be seen as *referential* performances, for they involve the language—world relation (=reference) as mediated by visual perception. In contrast, naming from definition and verbal matching are *inferential* performances, as they exclusively involve the semantic properties of words and sentences. In what follows, we shall use 'inferential naming' − InfNam for the definition-to-noun task, and 'referential naming' − RefNam for the picture-to-noun task. Accordingly, word-to-picture matching tasks (such as selecting the picture of a carrot as corresponding to the word 'carrot') are considered as referential tasks, while word-to-word matching tasks are considered as inferential. It could be remarked that written or spoken words, like pictures, must be perceived to be processed. This is, of course, correct; however, it does not follow that the tasks we regard as inferential are really referential or that there is no significant distinction between both kinds of task. It is one thing to relate (perceived) words to other words, and a different thing to relate pictures (or objects) to words or words to pictures, though perception is involved in both cases, at some stage.

Let us now consider the neuropsychological evidence in some detail.

1.1. Spared inferential, impaired referential processing

In a number of cases, impaired referential tasks (e.g., picture naming and/or word-to-picture matching) go together with good or even excellent inferential abilities. Most cases of "optic aphasia" fall within this category. For example, JB, a patient reported by Riddoch and Humphreys (1987b) scored 45.5% on naming from vision and obtained an accuracy of 70% on a word-to-picture matching with target and distractors which were visually and semantically similar (100% when

target and distracters were dissimilar). Interestingly, he was 100% correct in two inferential tasks, matching words to definitions and word–word matching task (coordinate matching). Several other cases of preserved inferential abilities, going together with referential deficits of some kind, have been reported (Farah et al., 1991; Hart and Gordon, 1992; Lhermitte and Beauvois, 1973; Warrington, 1975). It should be noted that picture naming has been found to dissociate from word-to-picture (and word-to-object) matching. Thus e.g., patient EST, who showed a deficit in naming but, was 97% correct on word-to-picture matching (limited to concrete words, Kay and Ellis, 1987). Another patient, KR, was 100% correct on word-to-picture matching in spite of a profound naming deficit (limited to animals, Hart and Gordon, 1992); similarly, SF, whose naming performance was poor (between 20.8% and 23.3% correct), could draw objects from their names and selectively match pictures to words (Lhermitte and Beauvois, 1973; Lucchelli and De Renzi, 1992; Miceli et al., 1991; Riddoch and Humphreys, 1987a). By contrast, patient DT exhibited the complementary deficit: "When single pictures of objects were presented he immediately named them (9/10); when he was requested to point to one of two pictures in a word-[to-] picture matching task, he named both of them, pointing at random" (Silveri and Colosimo, 1995). These findings motivated one of us to draw a distinction within referential competence, between a naming ability that would be responsible for naming performances and an application ability, that would be responsible for performances such as word-to-picture and word-to-object matching (Marconi, 1997). There are, however, some cases in which inferential processing has been found to dissociate from both kinds of referential processing (e.g., Riddoch and Humphreys, 1987b; Warrington, 1975).

1.2. Spared referential, impaired inferential processing

The complementary dissociation (selective preservation of referential abilities) is definitely less frequent. Preserved visual naming in a patient with severe single word comprehension impairment, as assessed with inferential tasks, was first reported by Heilman et al. (1976), who attributed this clinical picture to a unidirectional disconnection from Wernicke's area to the "concept centre". A similar case was reported by the same author in 1981 (Heilman et al., 1981). Kremin (1986) described the case of ORL, a patient afflicted with a metastatic lesion involving the left frontal lobe. Though ORL's RefNam performance for both real objects and pictures was close to perfect (95–100%), and spoken word-to-picture matching was fair (66% in a four choices task), she was severely impaired both in auditory pairing synonyms and in word association (12% correct in the latter). In addition she was impaired in a picture – picture matching task (48%). Shuren et al. (1993) reported a case of a patient (patient 3) with a diagnosis of Alzheimer's Disease (AD), who showed preserved visual naming (100%) and word-to-picture matching (98.33% vs 100% in controls). Otherwise, the same patient showed an impairment in definition-to-noun tasks (one predominantly based on associative information, 79% vs 98–99% in controls, the other on structural information, 67% vs 97%–87% in controls). The syndrome, labeled "nonoptic

aphasia", was attributed to the preservation of a direct route going "from the internal visual representations to the lexicon", bypassing the semantic system. Other AD patients with relatively preserved RefNam and poor verbal processing were more recently reported by Visch-Brink et al. (2004 cases 1, 2 and 3), though in this study word-to-picture matching performance was not investigated.

As in the case of the opposite dissociation, in some patients, when inferential abilities are lost or severely impaired, it is either RefNam (Brennen et al., 1996) or word-to-picture matching (Hart and Gordon, 1992; Hittmair-Delazer et al., 1994; Semenza and Zettin, 1989) that is preserved.

To summarize, the selective impairment of referential abilities is not uncommon, and is characteristic of optic aphasia. In the latter condition RefNam from vision is typically lost or impaired, whereas InfNam from definition is typically preserved. In the case of optic aphasia, the dissociation has been explained by hypothesizing two or more separate semantic domains, e.g., "visual" and "verbal" (Beauvois, 1982). On an alternative hypothesis, though the semantic system is unitary and need not be organized in separate subdomains, there are "privileged relationships" between certain types of input and semantic representation as such: e.g., access to semantic representation from vision is bound to privilege perceptually salient features of objects or pictures (Caramazza and Hillis, 1990; see Caramazza and Mahon, 2006 for further discussion). The much rarer cases of selective inferential impairment have been interpreted as the consequence of selective lexical semantic impairment, bypassed by a direct route from visual processing to the lexicon.

Additional neurological evidence for the distinction between referential and inferential can be derived from neuroimaging studies investigating semantic memory. Most of these studies, however, have focused on the distinction between different types of materials (i.e., verbal vs nonverbal), presented through the visual (Bright et al., 2004; Moore and Price, 1999; Vandenberghe et al., 1996; Vandenbulcke et al., 2006) and auditory (Dick et al., 2007; Thierry et al., 2003; Visser and Lambon Ralph, 2011) modalities. It is clear that the inferential versus referential distinction does not exactly map onto the verbal-nonverbal distinction. While inferential tasks are exclusively verbal, referential tasks, such as word-to-picture matching, involve both verbal and nonverbal material. Nevertheless, both classes of tasks are considered as "verbal" in the imaging literature, while non verbal tasks are typically based on the matching of pictures or nonverbal sounds.

Following this distinction, several studies have highlighted, in addition to a common left lateralized semantic network, material-specific activations, involving left hemispheric regions for verbal stimuli and right hemispheric regions for nonverbal stimuli (Thierry et al., 2003; Thierry and Price, 2006; Vandenberghe et al., 1996 as reanalyzed by Thierry and Price, 2006; Vandenbulcke et al., 2006). Specifically, some authors found that left middle and superior temporal regions were selectively more involved for verbal material, while the right midfusiform and right posterior middle temporal cortex were selectively more involved for nonverbal processing (Thierry and Price, 2006; Vandenberghe et al., 1996 as in Thierry and Price, 2006; and for converging evidence in patients with neurodegenerative pathologies see Butler et al., 2009).

As discussed above, the dichotomy between verbal and nonverbal materials refers to the presence or absence of words as stimuli. However, this dichotomy does not include conditions in which both types of materials are considered (namely the referential conditions). The impact of increasing/decreasing amount of verbal information in input has been addressed by a recent functional Magnetic Resonance Imaging (fMRI) study (Hocking and Price, 2009), using an audiovisual matching task. Subjects were asked to indicate if two stimuli, simultaneously presented in both the auditory and the visual modality, referred to the same object or not. Four experimental conditions were adopted combining the two types of material (verbal and nonverbal): verbal—verbal (spoken word-written word), verbal-nonverbal (spoken word — photography), nonverbal-verbal (written word-environmental sound), nonverbal—nonverbal (environmental sound-photography). The left superior temporal sulcus was more involved as verbal content increased, the right fusiform gyrus (RFG) with nonverbal material (decrease of verbal information). Some of the conditions used in this study can be considered as inferential (involving only words, verbal—verbal condition) or referential (involving both words and pictures or sounds, verbal—nonverbal and nonverbal—verbal conditions) within our conceptual framework. This study does not make it clear whether the hemispheric asymmetry for material type remains significant when only verbal information (inferential tasks) is directly compared with information containing both verbal and nonverbal material (referential tasks). In addition, stimuli were not presented in the same modality, therefore the differences could be affected by cross modal integration processes.

Evidence from studies of patients with semantic dementia with left/right asymmetry of atrophy appears to support the hemispheric asymmetries involving the verbal versus nonverbal dichotomy. Recently some research showed that nonverbal tasks are more affected by right temporal damage (Butler et al., 2009; Ikeda et al., 2006; Mion et al., 2010; but see Thompson et al., 2003), verbal tasks by left temporal damage (Hosogi Senaha et al., 2007; Mion et al., 2010; Thompson et al., 2003).

Finally, evidence derived from the study of patients with semantic dementia performing referential tasks, such as picture naming and word-to-picture matching may also be relevant. Patients with greater left than right temporal atrophy were more impaired than patients with greater right than left atrophy on both referential tasks (Thompson et al., 2003) or on picture naming only (Mendez et al., 2011). In addition, Mion et al. (2010) showed that the left anterior fusiform metabolism most contributed to predicting scores on picture naming and category fluency, whereas the right anterior fusiform metabolism was most responsible for scores on a nonverbal test (picture—picture matching). Some additional evidence points to a role of the right temporal lobe for referential tasks. Patients with semantic dementia with predominately left temporal atrophy were more impaired in naming objects than in word-to-picture matching, while those with greater right temporal involvement showed a similar impairment for both referential tasks (Lambon Ralph et al., 2001).

Thus, the way in which the right and left temporal lobes contribute to inferential versus referential processing remains unclear. The fMRI study reported by Tomaszewki Farias et al. (2005) could be considered relevant for the present issue. They had 10 healthy right-handed participants performing a RefNam task (naming line drawings from the Boston Naming Test), and 10 additional participants performing a naming to definition task. Two participants performed both tasks. The tasks were found to be associated with distinct activation patterns. The picture naming task, which according to the distinction proposed here is referential, compared to the inferential, naming to verbal description task, resulted in significant activations in several extra-temporal sites, including the cuneus and middle occipital gyri, as well as some other areas, including the insula, cingulate, parahippocampal, and inferior parietal gyri. In general, the picture naming task was associated with greater activation of the right hemisphere as compared with the definition-to-noun task. In contrast, the naming to verbal description task resulted in significant activations within the inferior, middle, and superior temporal gyri of the dominant hemisphere. Other areas outside of the temporal lobe were also identified in this contrast, most notably in the inferior frontal lobe. The results are partially in line with the hemispheric asymmetries reflecting the verbal versus nonverbal dichotomy.

The available evidence is compatible with the hypothesis that the neurological mechanisms involved in referential and inferential semantic processing at the single word level can be differentiated, independent of specific task requirements. In order to confirm this hypothesis, and to identify the brain structures that can differentiate these abilities, it is necessary to directly assess the brain activity associated with comparable tasks (naming and matching), involving, respectively, referential and inferential processing.

This is the aim of the present fMRI study. We hypothesize that (1) partially different areas are involved in inferential versus referential processing as such, (2) the difference persists across different kinds of task (naming *vs* matching). In particular, as inferential tasks only involve words and sentences as stimuli, we expect these tasks to engage brain regions associated with language processing more than referential tasks do. In contrast, referential tasks, constituted by an association between words and pictures, might recruit some of the same areas engaged by inferential tasks in that they involve the processing of linguistic materials, but also areas reported to be specific for nonverbal tasks. If this is the case, it is further possible that the difference between referential versus inferential processing may involve hemispheric asymmetries, i.e., left hemispheric inferential, and right hemispheric referential.

To date, no study has directly compared tasks involving both pictures and words with tasks involving only words. The tasks employed in this study are among those most frequently used with neuropsychological patients, allowing to relate the results of this study with the neuropsychological literature.

2. Experimental methods

2.1. Subjects

A group of 23 subjects (mean age = 22 years; mean education = 13 years) participated in the experiment. All

subjects were native Italian speakers and had normal or corrected-to-normal visual acuity. Participants reported being free of neurological disorders or history of seizures. All were right handed, with a mean score on the Edinburgh Handedness Inventory of +95 (Oldfield, 1971). Participants were informed about the procedures and informed consent was obtained after a safety screening. The experimental methods had ethical approval from the local Human Ethics Committee.

2.2. Behavioral procedure

To test our experimental hypothesis, four experimental tasks and one baseline condition (B) were included in the experimental design. The experimental conditions could be categorized according to two dimensions, processing modality (inferential or referential) and type of task (naming or matching). Two referential tasks involved pictures (picture naming, i.e., RefNam, and word-picture matching, i.e., referential matching − RefMat), while the two inferential tasks involved only words (naming by definition, i.e., InfNam, and word−word matching, i.e., inferential matching − InfMat).

2.2.1. Stimuli
For the picture naming task 48 pictures were selected from the Viggiano et al. (2004) battery. In the word-picture matching task 48 more pictures from the same battery were used as target pictures, while 96 were used as distracters. Importantly, there was no overlap between the pictures used during picture naming and word-picture matching task. For the naming by definition task the target words were selected in the medium range of frequency (De Mauro et al., 1993) and the definitions were built according to a rating performed on 30 young subjects that were asked to complete the InfNam task on an extensive list of stimuli. For the construction of the word−-word matching task the distracters were selected in order to leave no ambiguity in the selection of the target word. Items were coded for a number of variables known to influence general difficulty (word frequency, word length and familiarity) and the task blocks were balanced on these basis. Independent sample T-tests showed no significant differences ($p > .05$) in any of the coded variables between the experimental blocks (eight for each task) and between the four principal conditions (RefNam, InfNam, RefMat, InfMat). Furthermore, an equal number of living and non-living items (for both words and pictures) were included in each experimental block and in each principal condition.

The word stimuli were presented in black lower-case letters (Arial font size 42) on a white background, while the pictures had a size of about 7×7 cm^2 and a resolution of 300×300 dpi in all tasks involving images.

Each task began with the instruction [RefNam: "Denomina le immagini!" (Name the pictures!); InfNam: "Denomina!" (Name it!); RefMat: "Scegli l'immagine!" (Choose the picture!); InfMat: "Scegli l'associazione!" (Choose the association!); B: "Guarda!" (Look at it!)] presented for 1000 msec and followed by a 1000 msec delay. For each of the four experimental tasks, blocks of six trials were presented for 4000 msec each and with an inter-trial interval of 2000 msec. During the B condition a fixation cross was presented for 34000 msec and was followed by a 2000 msec delay. This structure generated task blocks of 38 sec each (including instruction), for all the conditions.

Concerning the RefNam task, one picture was displayed in the center of the screen, while in the InfNam task a sentence was presented in the center of the screen; in both the naming tasks the subjects had to look at the stimulus and to overtly name the pictured object or the object corresponding to the definition. In the RefMat task a word was shown at the top center of the screen and the three possible pictures were presented underneath on the left, center and right; the subjects were asked to select, by a button press, the picture corresponding to the word being shown. Finally, in the InfMat task the target word was presented at the top center of the screen while the three words were displayed underneath on the left, center and right; the subjects had to choose, by a button press, the word most closely related to the target word. During the B condition the subjects were simply asked to look at the fixation cross displayed at the center of the screen.

During each experimental condition, subjects were instructed to respond as fast as possible. During naming tasks, participant responses were delivered through a plastic tube from inside the scanner to a microphone connected to a computer, outside the scanner room. During the matching tasks, the subjects made a speeded response decision via a three-choice button press, using three fingers, selecting one of the three displayed words or pictures depending on their position on the screen (left, center or right).

2.3. fMRI procedure

Four runs were constructed for fMRI acquisition. Each run included two RefNam blocks, two InfNam blocks, two RefMat blocks, two InfMat blocks and two B blocks. Each run lasted about 6 min. The order of the experimental blocks within each run was pseudo-randomized, such that there were never two consecutive blocks of the same task, and the order of presentation of the runs was fully randomized across subjects.

At the foot of the magnet bore, a translucent screen was placed to which stimuli were delivered via a projector connected to a laptop outside the magnet room. Presentation 10.1 (Neurobehavioral Systems, Albany, CA, USA) was used for the presentation of stimuli and response collection. A mirror system inside the magnet room allowed the participants to view the translucent screen from inside the magnet. Participants were trained to minimize head, jaw and tongue movement while naming in order to reduce the amount of movement artefacts. In order to control for motor activations, half the subjects used the right hand and half the left hand for the two tasks involving a finger press. A computer recorded both button responses and voice onset times (VOT) via Presentation.

2.3.1. Behavioral data
A repeated measure of analysis of variance (ANOVA) on both accuracy and reaction times (RTs) was conducted to investigate differences between the four tasks. Post-hoc analyses (Bonferroni correction) followed in order to explore the significant differences.

2.3.2. Image acquisition

An fMRI technique was used (3T Intera Philips body scanner, Philips Medical Systems, Best, NL, 8 channels-sense head coil, SENSE reduction factor = 2, TE = 30 msec, TR = 2000 msec, FOV = 240 × 240, matrix size = 128 × 128, 30 contiguous axial slices per volume, 210 volumes for each run, slice thickness = 4 mm). Whole-brain functional images were obtained with a T2*-weighted gradient echo, echo-planar sequence, using blood-oxygenation-level-dependent contrast. Ten dummy scans preceded each run, all of which were then discarded prior to data analysis to optimize Echo Planar Imaging (EPI) image signal.

A high resolution structural MRI was obtained for all subjects during scanning (MPRAGE, 150 slice T1-weighted image, TR = 8.03 msec, TE = 4.1 msec; flip angle = 8°, TA = 4.8 min, resolution = 1 mm × 1 mm × 1 mm) in the axial plane. Statistical Parametric Mapping (SPM5) (Wellcome Department of Imaging Neuroscience, London, UK), running on Matlab 6.5 (The Mathworks, Natick, MA, USA) was used for preprocessing and statistical analysis.

2.3.3. Image pre-processing

Prior to analysis, all images for all the tasks underwent a series of preprocessing steps. Prior to realignment, time series diagnostics using tsdiffana (Matthew Brett, MRC CBU: http://imaging.mri-cbu.cam.ac.uk/imaging/DataDiagnostics) were conducted to ensure the quality of the functional data, as scans or slices that show deviations from time-series mean may be corrupt and need more detailed inspection. For each scanning run, then, all volumes were realigned to the first volume of the first run in order to neutralize effects of intra and intersession movements. Volume artefacts due to movement were detected in five subjects; bad volumes were repaired using the ArtRepair Toolbox (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm). This toolbox estimates volume artefacts and points out the volumes to be deweighted during the design matrix estimation. Bad volumes were determined based on scan-to-scan motion (1 SD change in head position) and outliers relative to the global mean signal (3 SD from the global mean). All repaired volumes were then deweighted as specified in the SPM design matrix. Additional volumes contiguous to large discontinuities in global intensity or movement even after repair were also deweighted as they could degrade the accuracy of the design matrix estimation. Mean EPI image of each participant was computed and spatially normalized to the Montreal Neurological Institute (MNI) single subject template (Collins et al., 1994; Holmes et al., 1998) using the "unified segmentation" function in SPM5. This algorithm is based on a probabilistic framework that enables image registration, tissue classification, and bias correction to be combined within the same generative model. The derived parameters of a discrete cosine transform, which define the deformation field deformations for each subject, were applied to the individual realigned EPI volumes, in order to bring them into a standardized MNI space.

All images were thus transformed into standard MNI space and re-sampled to 2 mm × 2 mm × 4 mm voxel size. Finally, the T2*-weighted volumes were smoothed using a Gaussian kernel with 8 mm full-width at half-maximum (FWHM), in order to account for any residual between-subject variation

and allow application of Gaussian random field theory to provide for corrected statistical inference and in order to increase the signal to noise (Friston et al., 1994). Data were highpass-filtered at 1/128 Hz and were then analyzed with a general linear model (GLM) as implemented in SPM5. Temporal autocorrelation was modeled using an autoregressive (AR) (1) process.

2.3.4. fMRI analysis

We adopted a two-stage random-effects approach to ensure generalizability of the results at the population level (Penny and Holmes, 2003). At the individual level, pre-processed images were first analyzed with a GLM. For each participant, we modeled the four experimental tasks and the baseline task (RefNam, InfNam, RefMat, InfMat and B).

Contrast maps from individual subjects were then entered into a random-effects analysis to assess their significance at the group-level (n = 23 participants). The individual data consisted of the contrast maps (RefNam-B, InfNam-B, RefMat-B, InfMat-B) that accounted for the BOLD signal, which covaried with each of the four tasks as compared to baseline. For the second-level multi-subjects analysis, all contrast maps were entered in a multiple regression without constant term model analysis with five regressors: (1) (Main RefNam) a categorical regressor modeling the average BOLD amplitude produced by the RefNam task; (2) (Main InfNam) a categorical regressor modeling the average BOLD amplitude produced by the InfNam task; (3) (Main RefMat) a categorical regressor modeling the average BOLD amplitude produced by the RefMat task; (4) (Main InfMat) a categorical regressor modeling the average BOLD amplitude produced by the InfMat task; (5) (RTs) a linear regressor, modeling the differential RTs produced by each subject in response to the four different experimental tasks (RefNam, InfNam, RefMat, InfMat). This regression model accounted for the mean effect of each of the four tasks subtracted from B and allowed estimation of BOLD signal change specific to inferential or referential processes and not reflecting differences between RT patterns.

Hence, in this analysis, inferential semantic processing (INF) was defined in contrast to referential semantic processing (REF).

First, a "conjunction" procedure via inclusive masking was adopted to identify significant regions of a common network activated by inferential and referential tasks.

To identify regions involved in inferential processing common to referential processing we assessed the conjunction of the two inferential tasks (2 & 4) inclusively masking them with the conjunction of the two referential tasks (3 & 5) (at $p < .05$ uncorrected).

To highlight referential processing activations common to inferential processing we entered the two referential tasks (3 & 5) in a conjunction analysis inclusively masked with the conjunction of the two inferential tasks (2 & 4) (at $p < .05$ uncorrected).

With this masking procedure, results are restricted to regions inside the mask area (inclusive masking), enabling to highlight the common regions of activation for which voxels reached a higher t statistic than the value corresponding to a voxel-level Familywise Error (FWE)-corrected p value of .05 for the conjunction of the two inferential tasks or the two referential tasks.

The first contrast computed in the second-level analysis included both inferential tasks (InfNam and InfMat), to reveal the areas activated specifically during inferential processing as compared to referential processing (RefNam and RefMat).

The second contrast instead included the two referential tasks (RefNam and RefMat) to highlight areas specifically active for referential processing with respect to inferential processing. For instance, to compare INF with REF, we computed the following contrast −1 1 −1 1, which we refer to as INF-minus-REF, to simplify. To compare instead REF with INF we computed the contrast 1 −1 1 −1 which we refer to as REF-minus-INF.

Brain activation maps were thresholded at $p < .05$ corrected for multiple comparisons (FWE), and clusters with a minimum of 10 voxels were reported.

Parameter estimates (or average relative changes in BOLD) were generated in each task across INF and REF, to better illustrate the data at the voxels of interest. For local maxima of Z-scores in the clusters evidenced in the two contrasts, the MNI coordinates were reported.

3. Results

3.1. Behavioral data

There was an accuracy rate of 93.1% (SD = 7.2) in the RefNam task, of 88.6% (SD = 6.5) in the InfNam task, of 99.5% (SD = .9) in the RefMat task and of 97.7% (SD = 2.8) in the InfMat task. A repeated measures ANOVA underlined that there were significant differences in correct responses between the four tasks [F(1,3) = 25.81, $p < .0001$]. Post-hoc analyses highlighted that both matching tasks were easier than naming task

(RefMat vs RefNam: $p < .0001$; RefMat vs InfNam: $p < .00001$; InfMat vs RefNam: $p < .008$; InfMat vs InfNam: $p < .00001$); in addition, the RefNam task was performed better that the InfNam task ($p < .01$).

As far as RTs are concerned, mean Rts were 1328.6 msec (SD = 265.5) for the RefNam task, 2759.1 msec (SD = 455.0) for the InfNam task, 1106.4 msec (SD = 236.9) for the RefMat task and 1964.6 msec (SD = 374.2) for the InfMat task. A repeated measures ANOVA underlined that RTs differed between the four tasks (F (1, 3) = 319.9, $p < .01$). Post-hoc analyses (Bonferroni correction) highlighted that the subjects were faster during RefMat than during all the other tasks (RefMat vs RefNam: $p < .002$; RefMat vs InfNam: $p < .001$; RefMat vs InfMat: $p < .0001$). Furthermore, performance on RefNam was significantly faster than on the InfNam and InfMat tasks (RefNam vs InfNam: $p < .001$; RefNam vs InfMat: $p < .0001$), while in the InfMat task RTs were faster than on the InfNam task ($p < .0001$).

3.2. fMRI results

3.2.1. Common network
The conjunction − masking procedure for inferential tasks revealed a bilateral network of brain areas, including the precentral and postcentral gyri, the inferior frontal gyrus (pars orbitalis) and the superior temporal gyrus. Additional activations in the left hemisphere included the middle and inferior temporal gyri, the temporal pole, the inferior occipital gyrus and cerebellum. Further activations in the right hemisphere were found in the calcarine gyrus and the lingual gyrus and the insula (see Table 1 for details).

The conjunction − masking procedure for referential tasks highlighted a bilateral activation of the cerebellum, the

Table 1 − Conjunction of the two inferential tasks ($p = .05$ FWE corrected) inclusive masked with the conjunction of the two referential tasks ($p = .05$ uncorrected). Multiple peaks within a cluster are shown on subsequent lines. Voxels p values are provided for FWE correction for multiple comparisons.

Regions	Cluster extent	Voxel level		Coordinates		
		P corrected	Z	x	y	Z
Bilateral clusters						
Right calcarine gyrus	2632	.000	Inf	16	−92	4
Left inferior occipital gyrus		.000	7.52	−20	−92	−8
Left cerebellum		.000	7.07	−20	−64	−24
Left hemisphere clusters						
Inferior temporal gyrus	242	.000	6.55	−52	−8	40
Postcentral gyrus		.000	6.39	−54	−12	32
Precentral gyrus		.000	6.28	−40	−8	36
Inferior frontal gyrus (pars orbitalis)	76	.000	6.18	−36	30	−4
Middle temporal gyrus	65	.000	5.89	−62	−20	−4
Superior temporal gyrus	23	.002	5.32	−38	−30	0
Precentral gyrus	14	.005	5.15	−52	0	20
Temporal pole	11	.006	5.13	−52	14	−16
Thalamus	17	.010	5.00	−6	−26	−4
Right hemisphere clusters						
Insula lobe	23	.005	5.13	42	24	0
Inferior frontal gyrus (pars orbitalis)		.010	5.00	36	22	−12
Lingual gyrus	28	.007	5.07	18	−30	−8
Precentral gyrus	54	.008	5.06	46	−4	32
Postcentral gyrus		.008	5.04	58	−10	24
Superior temporal gyrus	16	.011	4.98	50	−22	0

Table 2 — Conjunction of the two referential tasks (p = .05 FWE corrected) inclusive masked with the conjunction of the two inferential tasks (p = .05 uncorrected). Multiple peaks within a cluster are shown on subsequent lines. Voxels p values are provided for FWE correction for multiple comparisons.

Regions	Cluster extent	Voxel level		Coordinates		
		P corrected	Z	x	y	Z
Bilateral clusters						
Left SMA	91	.001	5.53	0	2	60
Right SMA		.001	5.44	2	0	68
Left hemisphere clusters						
Middle occipital gyrus	13	.000	5.87	−28	−76	12
Cerebellum	11	.001	5.61	−16	−30	−28
Fusiform gyrus	10	.001	5.49	−38	−46	−8
Putamen	12	.004	5.23	−22	18	8
Caudate nucleus		.009	5.02	−22	26	4
Thalamus	10	.006	5.11	−6	−20	12
Right hemisphere clusters						
Cerebellum	3724	.000	7.78	34	−68	−24
Lingual gyrus		.000	7.49	6	−94	−12
Fusiform gyrus		.000	7.43	40	−46	−24
Thalamus	27	.002	5.39	4	−8	12
Inferior frontal gyrus (pars orbitalis)	26	.003	5.28	36	30	−8
Insula lobe		.011	4.98	40	24	4

fusiform gyrus, the supplementary motor area (SMA) and the thalamus. Additional activations included the left middle occipital gyrus, the right lingual gyrus and the right inferior frontal gyrus (pars orbitalis), putamen, caudate nucleus and insula (see Table 2).

3.2.2.   Inferential versus referential processing

Specific activations for inferential processing (compared with referential one) involved mainly the left hemisphere and included the middle and superior temporal gyri and the precentral gyrus. In addition, a significant cluster of activations was found in the right superior temporal gyrus. The

Table 3 — Brain areas active in the contrast inferential minus referential. All voxel significant at p < .05 FWE corrected. Multiple peaks within a cluster are shown on subsequent lines. Voxels p values are provided for FWE correction for multiple comparisons.

Regions	Cluster extent	Voxel level		Coordinates		
		P corrected	Z	x	y	Z
Left hemisphere						
Middle temporal gyrus	86	.000	5.66	−58	−34	0
Superior temporal gyrus		.015	4.90	−62	−38	12
Middle temporal gyrus	16	.010	5.01	−60	−18	−12
Precentral gyrus	14	.015	4.90	−42	2	40
Right hemisphere						
Superior temporal gyrus	14	.006	5.10	56	−24	8

coordinates and the Z-scores of the activated regions are listed in Table 3. Parameter estimates at significantly activated voxels showed that activity in the left middle temporal gyrus was specifically increased for both inferential tasks (InfNam and InfMat). Representative parameter estimates are shown in Fig. 1.

3.2.3.   Referential versus inferential

Referential versus inferential processing did not yield significant activations at the threshold of p < .05 FWE corrected at the whole brain level. Our a priori prediction was that referential tasks, constituted by an association between words and pictures, would recruit the RFG, which has been reported to be specific for nonverbal tasks in both control (Thierry and Price, 2006; Vandenberghe et al., 1996 as reanalyzed by Thierry and Price, 2006; Vandenbulcke et al., 2006; Hocking and Price, 2009) and patient studies (Butler et al., 2009). Table 4 reports the peak coordinates localized in the RFG highlighted in the aforementioned studies. To get an unbiased estimate of activation from the RFG for the four tasks (two REF and two INF) employed in this study, we created an 8 mm radius spherical Region of Interest (ROI) that was centered on the median of the x, y and z coordinates (44, −46, −22) reported for the RFG in the studies summarized in Table 4. The mean distance of coordinates reported in the studies included in the table from the center of our RFG spherical ROI (44, −46, −22) (calculated as the average of the mean absolute values of the difference in mmsec between each x, y and z value reported in the table and the x, y and z coordinates of the RFG ROI) was 2444 mmsec with a standard deviation of 2.32 mmsec (min = 0 mmsec; max = 8 mmsec).

The RFG ROI was then used to extract mean activation estimates (eigenvalues) from the four contrast images coding the main effects of each task (Main RefNam, Main InfNam, Main RefMat, Main InfMat) for each participant (N = 23) using SPM5 Easy-ROI toolbox (http://www.sbirc.ed.ac.uk/cyril/). Those estimates were then entered into a 2-by-2 ANOVA with the factors COGNITIVE PROCESS (referential or inferential) and TYPE OF TASK (naming or matching) in SPSS (SPSS Inc., Chicago, IL). This analysis revealed a significant main effect of both factors, i.e., COGNITIVE PROCESS [F (1,22) = 52.35, p < .001] and TYPE OF TASK [F (1,22) = 74.02, p < .001]. Pairwise comparisons adjusted for multiple comparisons (Bonferroni corrected) revealed that estimates of activation were significantly higher for referential (mean = 5.65; SE = .42) than inferential processing (mean = 2.90; SE = .35) and that activation in the RFG was significantly higher for matching (mean = 5.38; SE = .37) than naming tasks (mean = 3.18; SE = .37). The COGNITIVE PROCESS × TYPE OF TASK interaction did not reach significance [F (1,22) = 1.94, p < .18]. Inspection of activity in the RFG decomposed for COGNITIVE PROCESS revealed that referential processes induced significantly more activity in the RFG ROI irrespective of the task — picture naming (REFnam) (Mean Difference = +2.39; p < .001) or picture matching (REFmat) (Mean Difference = +3.11; p < .001) (see Fig. 2).

3.2.4.   RTs

RTs show a significant correlation only with the anterior intraparietal sulcus (see Table 5).
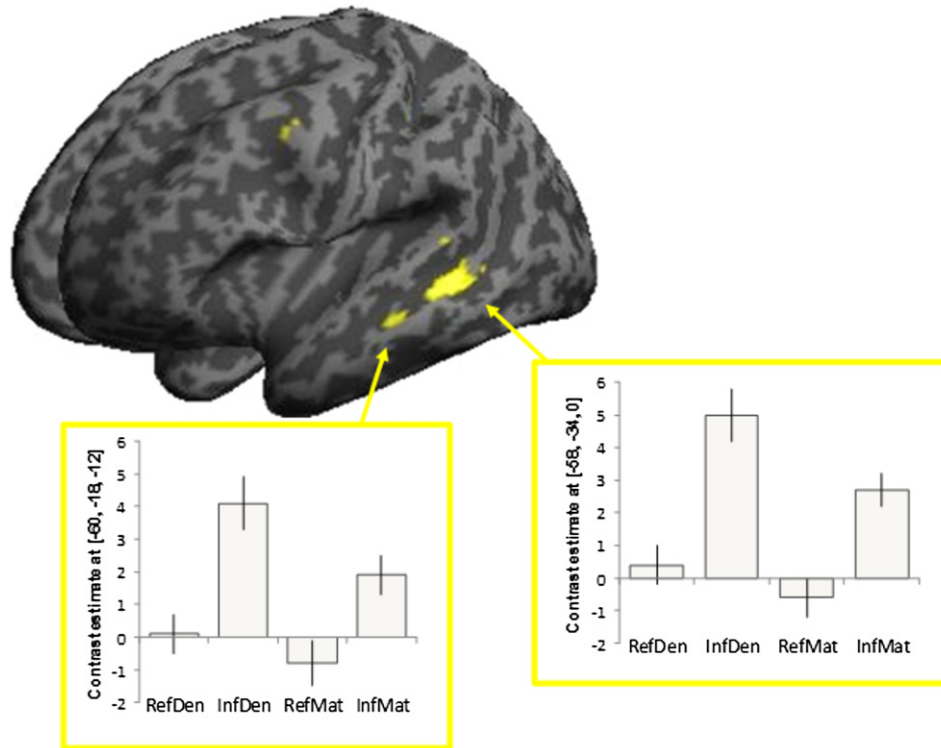
Fig. 1 – Functional data for inferential (INF) minus referential (REF) (yellow) are overlaid over a 3D render of the brain using the SPM canonical mesh. (in MNI space) distributed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/; Welcome Department of Imaging Neuroscience, London). Plots of parameter estimates for the four tasks (REFNam, INFNam, REFMat, INFMat) at peak coordinates for activation in the left middle temporal gyrus.

4. Discussion

In the first place, our findings indicate that inferential and referential processes engage a common network of brain areas. This network largely corresponds to the "common semantic system" outlined by many functional imaging investigations (for an extensive review see Binder et al., 2009). In other words, multiple brain regions are activated by any task that requires access to semantic knowledge. It is particularly noteworthy that areas associated with visual processing are engaged even when the modality of input is purely verbal (as with both inferential tasks), suggesting that access to visuoperceptual information can also be observed in the absence of any pictorial input.

We also found areas selectively engaged by inferential processes, and, at a lower threshold, by referential processing. The recruitment of left hemispheric brain regions, involving some classical language areas Middle Temporal Gyrus (MTG), appears to be specifically required only by inferential processing, while activations in right visual/semantic processing areas Frontal Gyrus (FG) were associated with referential processing. The imaging results thus provide some evidence in favor of the hypothesis that the type of processing

Table 4 – Peak coordinates localized in the RFG.

	Reference article	Coordinates for RFG			Difference	Task
		x	y	z		
Controls						
	Vandenberghe et al., 1996 [a]	40	−40	−20	Pictures > words	Semantic decision task
	Thierry and Price, 2006	46	−46	−22	Nonverbal > verbal (over modalities)	Categorization,
		44	−48	−26	Auditory modality	sequence interpretation task
		46	−44	−20	Visual modality	
	Vandenbulcke et al., 2006	45	−54	−24	Task-modality interaction	Associative-semantic task,
		36	−51	−21	Picture:associative *vs* visuoperceptual	visuoperceptual judgment
		42	−48	−27	Task-modality interaction[b]	
Patients	Hocking and Price, 2009	42	−46	−22	Nonverbal > verbal	Audiovisual matching task
	Butler et al., 2009	44	−42	−22	Picture > words	Associative-semantic task
		44	**−46**	**−22**	*Median coordinates difference RFG*	

a As reanalyzed by Thierry and Price (2006).
b Highly significant – no difference in RTs and accuracy between tasks.
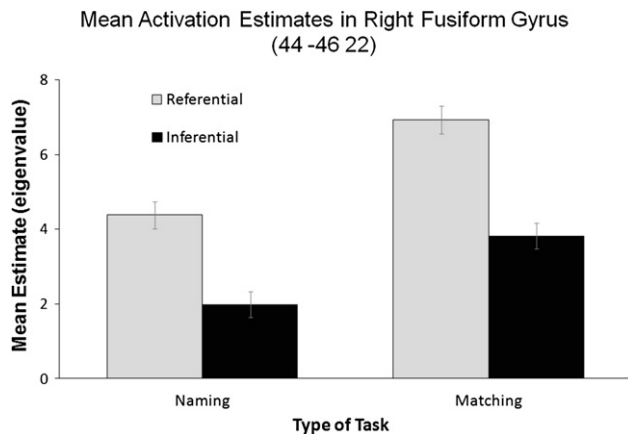
Fig. 2 – Mean activation estimates (with standard error bars) extracted in the RFGROI from the four contrast images relative to the main effect of each referential and inferential task.

requirements (within the lexicon, or from the lexicon to the world) are associated with differences in brain activation, independently of task (naming *vs* matching). The clinical cases of selective impairment of inferential or referential processing would then be explained as reflecting selective damage or defective access to the "inferential" or the "referential" regions.

Selective impairment of inferential processing is mainly characterized by preserved RefNam, associated with defective performance in tasks such as naming from verbal definition, synonym matching, etc. This clinical picture has not been reported in classical neuropsychology and was actually described for the first time as "naming without comprehension" by Heilman et al. (1981, 1976), who explained it as a unidirectional disconnection from Wernicke's area to the concept center. Within a cognitive neuropsychological framework, a similar phenomenon was attributed to preserved functioning of a direct route from visual representations to the lexicon, bypassing the semantic system (Kremin, 1986). The present findings are compatible with the hypothesis that selective inferential impairment may require a sparing of the referential regions and a selective involvement of LH areas required by inferential processing in normally functioning brains. The regions that were engaged by inferential processing are part of the "classical language areas" in the left hemisphere perisylvian region. They thus provide additional evidence for the role of specific components of this region in aspects of linguistic processing that go

beyond the lexical requirements of word-to-picture matching and picture naming. The temporal area of activation was centered in the middle temporal gyrus, that may be considered to reflect the additional demands on lexical and sentence processing posed by inferential, as contrasted with referential, tasks. The probability to observe effects of selective damage to the middle temporal gyrus may indeed be low because of the usual pathological mechanisms of vascular aphasia, which is often due to middle cerebral artery strokes involving large parts of the perisylvian territory. Small infarctions limited to the middle temporal gyrus can be observed only in the case of embolic strokes. It may thus be relevant that most of the reported cases have diagnosis of AD, a condition in which neocortical damage may be relatively selective in the early stages of disease. One of the purest cases of dissociation (Case ORL) had a small focal lesion involving the inferior frontal gyrus, i.e., a region which is part of the classical lexical retrieval network (Kremin, 1986).

How to explain the most commonly reported dissociation, i.e., impaired RefNam with preserved inferential processing? This dissociation is found in the clinical syndrome of optic aphasia, a modality-specific naming disorder (Farah, 2004; Gil et al., 1985; Lhermitte and Beauvois, 1973; Riddoch and Humphreys, 1987b) characterized by impaired naming from vision associated with preserved visual recognition (demonstrated, for example, by gesturing the object's use), as well as with preserved naming from other modalities, such as touch and audition. The syndrome was originally reported by Freund (1889) and interpreted as the consequence of a damage to the left hemispheric optic pathways, associated with defective transmission of information from the right-sided visual areas to the left hemispheric language area (it should be noted that this is the same explanation as Dejerine (1892) will later provide for the syndrome of pure alexia). Optic aphasia has thus been classically considered as a disconnection syndrome between vision and semantics. The pattern of performance is problematic for the idea of a single semantic system, and has been considered to support the hypothesis of multiple semantic systems, either a visual and a verbal semantic system (Beauvois, 1982; Lhermitte and Beauvois, 1973) or a right hemisphere and a left hemisphere semantic system (Coslett and Saffran, 1989, 1992), which are "disconnected" in these patients. Other accounts have preserved the idea of a single semantic system, proposing that semantic representations exhibit graded functional specialization rather than being entirely amodal or modality-specific. Damage to connections from vision to regions of semantics near phonology is supposed to impair visual object naming far more than visual gesturing or tactile naming because of a topographic bias on learning favoring short connections, as well as of the non-systematic nature of naming in comparison, for example, to visual gesturing (Plaut, 2002). The idea is actually close to proposals that account for optic aphasia as a mild form of associative agnosia (De Renzi and Saetti, 1997) or as a form of partial semantic disorder (Hillis and Caramazza, 1995; Riddoch and Humphreys, 1987b). The present functional MR findings appear thus to be compatible with the classical disconnection account for the syndrome of optic aphasia, as well as with the possible selective involvement of the right temporo-occipital region. The right temporo-occipital region has been

Table 5 – Correlation between RTs and activations (p = .05 FWE corrected). Voxels p values are provided for FWE correction for multiple comparisons.

Regions	Cluster extent	Voxel level		Coordinates		
		P corrected	Z	x	y	Z
Left hemisphere						
Anterior intraparietal sulcus (hIP1)	86	.000	5.66	−32	−38	32

suggested to be the neural substrate of the structural description system, at the interface between visuoperceptual processing and semantic analysis (Zannino et al., 2011). In the patient described by Vandenbulcke et al. (2006) damage to this area was associated with defective retrieval of the visual attributes of both living and non-living entities. In the same paper, the authors reported a functional imaging study, showing that the same region was activated for the retrieval of visual features, but only when the input was pictorial rather than verbal. In these patients, inferential processing is preserved because access is possible from the auditory modality to the intact semantic processing areas.

In conclusion, the distinction between inferential and referential semantic processing proposed by Marconi (1997) appears to map on incompletely overlapping brain mechanisms. While a common set of brain areas is engaged by any task requiring access to semantic knowledge, additional left hemispheric regions are required in the case of inferential tasks, such as naming from definition and word matching. In addition, the right temporo-occipital cortex is selectively engaged by semantic access from pictorial information. These imaging findings are thus compatible with the clinical observations of double dissociation between referential and inferential abilities.

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