

Lateralization is Predicted by Reduced Coupling from the Left to Right Prefrontal Cortex during Semantic Decisions on Written Words

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Over 90% of people activate the left hemisphere more than the right hemisphere for language processing. Here, we show that the degree to which language is left lateralized is inversely related to the degree to which left frontal regions drive activity in homotopic right frontal regions. Lateralization was assessed in 60 subjects using functional magnetic resonance imaging (fMRI) activation for semantic decisions on verbal (written words) and nonverbal (pictures of objects) stimuli. Regional interactions between left and right ventral and dorsal frontal regions were assessed using dynamic causal modeling (DCM), random-effects Bayesian model selection at the family level, and Bayesian model averaging at the connection level. We found that 1) semantic decisions on words and pictures modulated interhemispheric coupling between the left and right dorsal frontal regions, 2) activation was more left lateralized for words than pictures, and 3) for words only, left lateralization was greater when the coupling from the left to right dorsal frontal cortex was reduced. These results have theoretical implications for understanding how left and right hemispheres communicate with one another during the processing of lateralized functions.

Keywords: dynamic causal modelling, effective connectivity, functional MRI, inter-hemispheric interactions, language laterality, semantic decision

Introduction

There is considerable interest in how and why language is lateralized to the left hemisphere in the majority of healthy individuals. One of the intriguing factors is that the degree to which language is lateralized varies from individual to individual. This has clinical implications for the effect of stroke or neurosurgical intervention because the effect of left hemisphere damage on language function may be less in those who have bilateral or right dominant language activation patterns (Springer et al. 1999; Woermann et al. 2003; Rijntjes 2006; Crosson et al. 2007). The aim of our study was to investigate how the degree to which language is lateralized to the left hemisphere is related to intersubject variability and how the left and right hemispheres interact with one another. We also tested whether the strength of the interhemispheric coupling between homologous (homotopic) language areas explained why laterality is stronger for verbal (word) stimuli than nonverbal (picture) stimuli (Geffen et al. 1971; Hines 1972; Beaumont 1997).

Our questions are motivated by previous proposals that 1) lateralization may be related to the degree to which the dominant hemisphere either inhibits or recruits the non-dominant hemisphere (Chiarello and Maxfield 1996; Bloom and Hynd 2005) and 2) interhemispheric interactions are stimulus dependent (e.g., Innocenti 2009) and may play an important role during the categorization of words and pictures (Koivisto

and Revonsuo 2003). However, although several models have been proposed to describe how the left and right hemispheres interact (e.g., Banich and Belger 1990; Cook and Beech 1990; Chiarello and Maxfield 1996; Belin et al. 2008), it is not yet known how these mechanisms operate during the processing of lateralized functions such as language (for review, see Stephan, Fink et al. 2007). Nor is there any mechanistic account of how laterality differences for verbal and nonverbal stimuli are related to interhemispheric coupling.

Interhemispheric interactions are an important facet of brain function because the task-specific activity generated by both hemispheres must be coordinated and integrated (Hoptman and Davidson 1994; Beaumont 1997; Banich and Weissman 2000). These interhemispheric interactions are complex (Clarke 2003), may emerge from different types of neuronal coupling (Nowak et al. 1995), and determine regional laterality (Bryden and Bulman-Fleming 1994; Hopkins and Rilling 2000) and selectivity (Doron and Gazzaniga 2008; Stark et al. 2008).

We tested the influence of interhemispheric connections on language lateralization using dynamic causal modeling (DCM) (Friston et al. 2003) to estimate the causal and directional influence of one hemisphere on the other during a semantic matching task with both verbal and nonverbal stimuli. Our semantic matching task was based on the "Pyramids and Palm trees" test, which is commonly used in clinical practice to assess semantic function (Howard and Patterson 1992). In brief, this semantic matching task requires access to detailed semantic information about words and pictures. For example, given a target word or picture such as "Pyramid," the participant selects another word or picture that is most closely associated to the target (e.g., palm tree vs. fir tree). Previous functional imaging studies have already reported strongly left-lateralized activation for this task relative to perceptual decisions (Vandenberghe et al. 1996; Seghier et al. 2004, 2008; Josse et al. 2008).

To keep the semantic content of the verbal and nonverbal stimuli constant, our nonverbal stimuli were pictures of objects and our verbal stimuli were the written names of the same objects. Nevertheless, semantic decisions on written words involves phonological processing that is not necessary for semantic decisions on pictures (Nelson and Castano 1984; Glaser WR and Glaser MO 1989). Left lateralization was therefore expected to be greater when the stimuli are in written rather than pictorial form (Vandenberghe et al. 1996; Perani et al. 1999; Postler et al. 2003).

As there is a limit on the number of regions that can be included in DCM analyses, we focused on 4 frontal lobe regions. This decision was based on clinical observations that the frontal lobes are the most reliable epicenters for language lateralization and on numerous functional imaging studies that

have shown a remarkable concordance between frontal activity and invasive laterality measures (Lehéricy et al. 2000; Spreer et al. 2002; Deblaere et al. 2004). Consistent with these prior observations, our preliminary analyses (see Experimental Procedures) also found that lateralization during our semantic matching task was most significant and consistent across subjects in the frontal lobes.

The robustness of DCM for assessing interhemispheric interactions has been demonstrated in many different contexts, including visual integration between left and right lingual and fusiform gyri (Stephan, Marshall et al. 2007), hand movement coordination between left and right motor cortices (Grefkes et al. 2008), processing of emotional speech melody (prosody) between left and right middle frontal gyri (Ethofer et al. 2006), and reading aloud between left and right occipital and angular gyri (Carreiras et al. 2009). There are 3 main motivations for using DCM in this study. First, it uses a biophysical forward model of hemodynamic responses that provides a more precise estimation of how the rate of change of activity in one region influences the rate of change in other regions (Friston et al. 2003; Friston 2009). This provides information about the direction of the interregional connections rather than implying a nondirectional correlation. Second, DCM can measure how each connection is modulated by an experimental factor (i.e., context-dependent connectivity). Third, a random-effects Bayesian model selection (BMS) procedure (Stephan et al. 2009; Penny et al. 2010) can be used to determine which combination of connections parameters best explains the data (i.e., identifying the most plausible models).

In summary, our aim was to explore how intersubject variability in language lateralization could be explained or predicted by interhemispheric functional connectivity. To maximize intersubject variability, our DCM analysis was conducted on a sample of 60 healthy adults who were either right-handed, left-handed, or ambidextrous. The DCM analyses focused on 2 left frontal regions (ventral and dorsal) and their right homologous counterparts, allowing us to characterize both intra- and interhemispheric interactions (see below). Using a systematic and unbiased procedure, our analyses focused on a series of hierarchical questions. First, we identified the circuitry of the DCM model that best explained our data. This involved determining whether the external inputs enter the model from ventral or dorsal frontal regions, whether the intrahemispheric interactions were forward or backward, and whether the interhemispheric interactions were unidirectional or bidirectional between left and right frontal regions. Second, we tested whether the endogenous connectivity for each connection in our best DCM model was significantly different from zero (i.e., an increase in activity in one region leading to a change in activity of the other region) and whether connections are similarly or differently modulated by words and pictures. Third, we correlated the amplitude of effective connectivity and laterality indices across subjects and compared the strength of this correlation for words versus pictures. Fourth, we investigated whether connectivity parameters were related to handedness, age, and/or response times.

Experimental Procedures

The study was approved by the National Hospital for Neurology and Institute of Neurology Joint Ethics Committee.

Subjects

The data from 60 healthy subjects (aged 32 ± 16 years, 29 females) were included in our DCM analyses. All gave written informed consent to participate, were native English speakers, had normal or corrected-to-normal vision, and had no history of neurological or psychiatric disorders. They had variable handedness (as assessed with the Edinburgh questionnaire; Oldfield 1971): 35 subjects were right-handed (score between 50 and 100) and 25 either left-handed or ambidextrous (score between -100 and 50). These 60 subjects were selected from a cohort of 98 subjects on the basis that they showed robust activations in all our regions of interest (ROIs), see Subject and ROI Selection below.

Task and Experimental Design

The semantic matching task was based on a visual categorization task commonly used in clinical practice. The task, known as “pyramids and palm trees” can be presented with pictures, written words, and/or auditory words (Howard and Patterson 1992); we used the written word and picture versions. Three stimuli are simultaneously presented, with the target item above and 2 test items below. The subject is required to indicate which of the 2 test items is most semantically related to the target. This task reliably identifies temporofrontal epicenters and language laterality (e.g., Vandenberghe et al. 1996; Josse et al. 2008).

The experimental design consisted of 2 separate scanning runs or sessions with the order of conditions counterbalanced within and across session. Each session consisted of 24 blocks of stimuli, each lasting 18 s, with an additional 12 blocks of fixation, each lasting 14.4 s and occurring every 2-stimuli blocks. Over the experiment, there were 4 conditions (see Fig. 2 of Josse et al. 2008): 1) semantic matching on written object names presented in 16 blocks, 2) semantic matching on pictures of objects presented in 16 blocks, 3) perceptual matching on unfamiliar Greek symbols presented in 8 blocks, and 4) perceptual matching on unfamiliar pictures of non-objects presented in 8 blocks. Each block was preceded by a written instruction (e.g., “match words” that stayed on the screen for 3.6 s). Each stimulus triad (trial) stayed on the screen for 4.32 s. Subjects were asked to indicate whether 1) the stimulus on the lower left or lower right was more semantically related to the stimulus above (e.g., is “truck” or “ship” most closely related to “anchor”) or 2), for the meaningless triads, was the lower-left or lower-right stimulus visually identical to the one above. Critically, by using written names and pictures that referred to the same object (e.g., horse), the verbal and nonverbal stimuli were matched for semantic content and associations.

Stimulus presentation was via a video projector, a front-projection screen, and a system of mirrors fastened to the Magnetic Resonance Imaging (MRI) head coil. Responses were recorded using a button box held under one hand throughout the experiment. Subjects who responded with the right hand ($n = 41$) indicated the lower-left stimulus with their first finger and the lower-right stimulus with their middle finger. Likewise, subjects who responded with their left hand ($n = 19$) indicated the lower-left stimulus with their middle finger and the lower-right stimulus with their first finger. The hand of response was not determined by the hand the subject used to write with. Approximately, half the left-handers responded with their right hand and the other half with their left hand. Likewise half

the adult right-handers responded with their left hand, but all the teenagers were right handed and responded with their right hand because the data were initially collected for a different study. Critically, however, the same hand of response was used in the semantic and perceptual conditions. Therefore, differences in left- and right-hand responders were removed when perceptual matching activation was subtracted from semantic matching activation. Indeed, post hoc analyses confirmed that the interhemispheric connectivity parameters from left dorsal inferior frontal gyrus (ldF) to right dorsal inferior frontal gyrus (rdF) that we report in the results were not related to the hand of response for the endogenous connectivity ($t = 0.14$, $P > 0.1$), word modulations ($t = 1.15$, $P > 0.1$), or picture modulations ($t = 1.07$, $P > 0.1$). Additional details about the paradigm and stimuli can be found in our previous work (cf., Josse et al. 2008; Hu et al. 2010).

To ensure that the task was understood correctly, all subjects undertook a short training session before entering the scanner with a different set of words and pictures.

MRI Acquisition

Experiments were performed on a 1.5-T Siemens system (Siemens Medical Systems). Functional imaging consisted of an EPI GRE sequence (repetition time/echo time/flip angle = 3600 ms/50 ms/90°, field of view = 192 mm, matrix = 64 × 64, 40 axial slices, 2 mm thick with 1 mm gap). Functional scanning was always preceded by 14.4 s of dummy scans to insure steady-state tissue magnetization. To avoid ghost-EPI artifacts, a generalized reconstruction algorithm was used for data preprocessing.

fMRI Data Analysis

Data processing and statistical analyses were performed with the Statistical Parametric Mapping SPM5 software package (Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm/>). All functional volumes were spatially realigned, unwarped, normalized to Montreal Neurological Institute (MNI) space using the unified normalization-segmentation procedure of SPM5, and smoothed with an isotropic 6-mm full-width at half-maximum Gaussian kernel, with resulting voxel size of 2 × 2 × 2 mm³. Time series from each voxel were high-pass filtered (1/128 Hz cutoff) to remove low-frequency noise and signal drift. The preprocessed functional volumes of each subject were then submitted to a fixed-effects analysis, using the general linear model at each voxel. Each stimulus onset was modeled as an event using condition-specific “miniblocks” having a duration of 4.32 s per trial and a stimulus onset interval of 4.5 s. These were convolved with a canonical hemodynamic response function, thus providing regressors for the linear model. The appropriate summary or contrast images were then entered into a second-level analysis (i.e., random-effects analysis) to enable inferences at the group level. From this second-level analysis, we generated statistical parametric maps of the t statistic at each voxel $SPM\{t\}$, which characterized differences in activation for any condition (i.e., semantic matching on words, semantic matching on pictures, perceptual matching on unfamiliar stimuli) relative to fixation.

Subject and ROI Selection

Prior to conducting the DCM analyses described below, a conventional second-level fMRI analysis was conducted on

our full sample of 98 healthy subjects to enable subject and region selection. The contrast of interest was “semantic matching on words and pictures relative to perceptual matching on unfamiliar symbols and nonobjects.” This identified robust left-lateralized semantic activations in ventral and dorsal inferior frontal regions, superior and middle temporal gyri, and the angular gyrus (see Fig. 1*a*), in line with numerous previous studies (e.g., Vandenberghe et al. 1996; Seghier et al. 2004, 2008; Josse et al. 2008).

Our 4 ROIs were extracted within the inferior frontal gyrus: left ventral inferior frontal gyrus (lvF) corresponding to pars orbitalis (Brodmann area (BA) 47) and its right homologue region (right ventral inferior frontal gyrus [rvF]) and ldF corresponding to pars triangularis (BA 44/45) and its right homologue region (rdF). Activation in all 4 regions was higher during semantic matching than perceptual matching (Fig. 1*a*) as observed in previous semantic matching imaging studies (e.g., Vandenberghe et al. 1996; Ricci et al. 1999; Roskies et al. 2001; Postler et al. 2003; Seghier et al. 2004; Cai et al. 2007). For instance, in a recent meta-analysis of semantic processing (Vigneau et al. 2006), frontal activation was identified in both ventral [coordinates at $x = -37$, $y = 31$, $z = -9$] and dorsal clusters [$x = -44$, $y = 21$, $z = 24$].

After defining our 4 ROIs (group peaks closest to those identified in Vigneau et al. 2006), eigenvectors (i.e., time series) were extracted from each subject’s individual activation map thresholded at $P < 0.05$ uncorrected at the closest maxima within a distance of 8 mm of the group peak voxel. This ensured that the functional regions included in the DCM models were as consistent as possible across subjects (for a similar rationale, see Stephan, Marshall et al. 2007; Seghier and Price 2010). If a participant did not have activation in 1 or more of our ROIs that satisfied our strict criteria, all data from that participant were excluded because DCM cannot compare models with different numbers of regions. From a cohort of 98 subjects, 60 were included because activation was recorded in all 4 of our frontal ROIs within a distance of 8 mm of the group peaks. The remaining 38 subjects were excluded because frontal activation was only identified in the left hemisphere ROIs (14/38), 3/4 of ROIs (12/38), or none of the ROIs (12/38). A second-level group comparison illustrated stronger and more extensive activation in the 60 included subjects than the 38 excluded subjects (see Supplementary Fig. 2). However, the reason that activation varied across subjects was unclear and not easily explained by known sources of variance (see Kherif et al. 2003; Miller and Van Horn 2007; Seghier et al. 2008). For example, the excluded subjects included 41% of the right-handers (24/58), 35% of the non-right-handers (14/40), 50% of the females (26/52), and 26% of the males (12/46). On average, the age of the excluded subjects was 32.4 ± 17 years and, according to Nagata’s laterality index (LI), see below for procedure, activation across the whole brain was left lateralized (LI = $+0.28 \pm 0.33$) with only 10% of the excluded subjects (4/38) having atypical lateralized activation (LI < -0.5) in the frontal regions.

These strict inclusion criteria ensured 1) a high degree of consistency across all 60 subjects (see Fig. 2*a*) and 2) robust activation in each ROI. Across our selected 60 subjects, the mean (\pm SD) of the MNI coordinates of our regions are: lvF = [$x = -36 \pm 4$, $y = 31 \pm 3$, $z = -14 \pm 3$], ldF = [$x = -50 \pm 4$, $y = 19 \pm 4$, $z = 27 \pm 4$], rvF = [$x = 34 \pm 3$, $y = 34 \pm 4$, $z = -10 \pm 4$], and rdF = [$x = 47 \pm 4$, $y = 20 \pm 4$, $z = 26 \pm 4$]. Data (principal

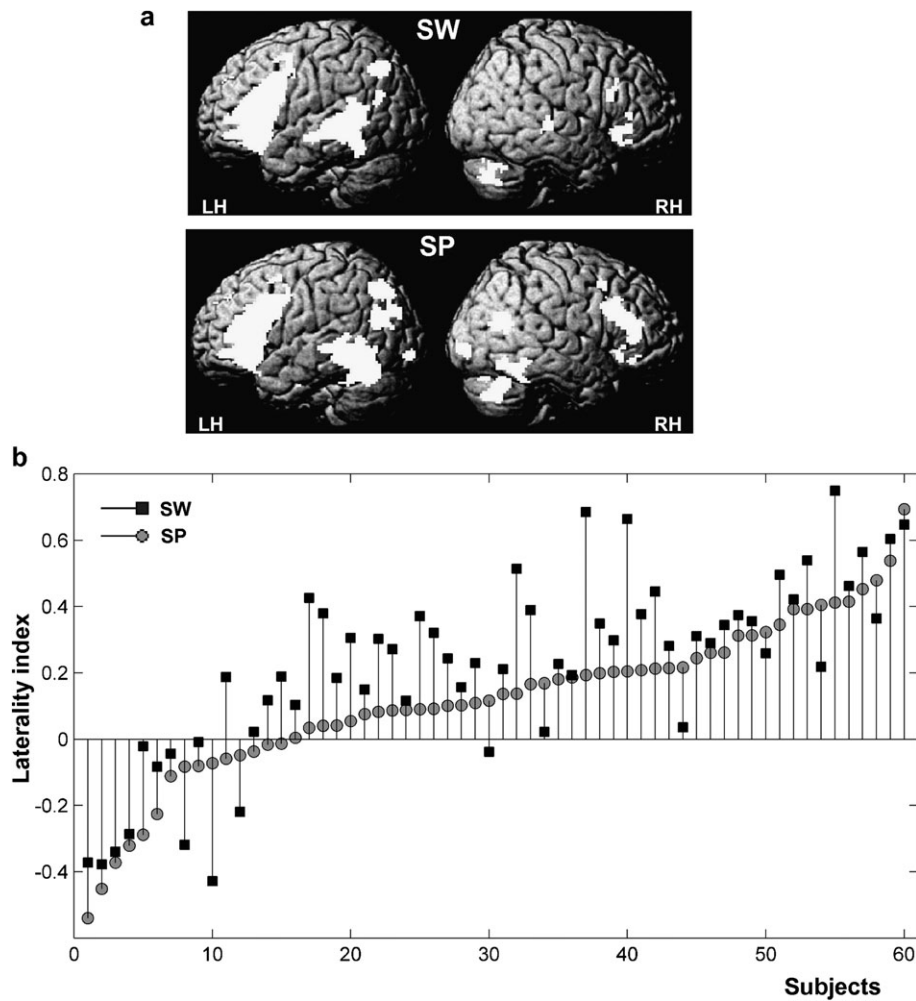


Figure 1. (a) Activation pattern from the group analysis (at $P < 0.001$ uncorrected) for semantic matching on words (SW) relative to perceptual matching on symbols (top) and semantic matching on pictures of objects (SP) relative to perceptual matching on pictures of nonobjects (bottom). (b) fMRI-based LI for both semantic matching on words (SW, in black squares) and pictures (SP, in gray circles), derived from a threshold-free method including all brain voxels. For illustration purposes, subjects 1–60 were sorted according to their LI during SW. LI values during SW are higher than SP ($t = 4.7$; $P = 0.00002$), as illustrated by the black squares being above the gray circles in the majority of our subjects. Forty-three subjects (71%) had left-lateralized responses for both words and pictures, and 37 of these (i.e., 86%) had stronger left lateralization for words than pictures. In the remaining 17 subjects, 13 (76%) had stronger LI values for words, even though the overall response was right lateralized. With respect to the 10 subjects who did not show stronger left lateralization for words than pictures, 7 were left-handed. Thus, there were only 3 (out of 35) right-handed subjects who did not show stronger left lateralization for words. Details of laterality indices irrespective of the volume of interest can be found in the Supplementary Material (Supplementary Table 1 and Supplementary Fig. 1).

eigenvariates) were extracted for each session separately within each ROI (4-mm-radius sphere) and adjusted to the F -contrast (i.e., effects of interest) of each subject. Then, the extracted ROI time series were concatenated over the 2 sessions and incorporated in the DCM model. Although many other regions participate in semantic matching tasks (e.g., Fig. 1a and Table 1), the inclusion of other regions is not needed to investigate our main hypotheses using the current deterministic implementation of DCM in SPM8 (e.g., see extended “stochastic” framework for modeling “missing regions” in Daunizeau et al. 2009).

Laterality Index

For each of our 60 healthy right- and left-handed individuals, we computed a threshold-free LI (Nagata et al. 2001) on 2 different contrasts that tested for 1) semantic matching on words relative to perceptual matching on symbols and 2) semantic matching on pictures of objects relative to perceptual matching on pictures of nonobjects. For each contrast, 2

different LIs were computed 1) across the whole hemisphere and 2) in the frontal ROIs only.

In brief, the approach of Nagata et al., to computing LI (Nagata et al. 2001; Seghier 2008), assesses the number of left and right hemisphere voxels activated for semantic matching relative to perceptual matching, at a wide range of different statistical thresholds. Nonlinear regression of the shape of the curve, describing the relationship between the number of voxels and the statistical threshold, provides a constant term that is used to compute a normalized difference between left and right hemisphere activity (see eq. 6 in Nagata et al. 2001). This procedure thus generates threshold-free LI values that take into account the activation level at different statistical thresholds. A positive LI (toward +1) indicates left hemisphere dominance, whereas a negative LI (toward -1) indicates right hemisphere dominance. The LI values of our 60 subjects are shown in Figure 1b and listed in Supplementary Table 1.

As shown in Figure 1b, the degree to which semantic matching responses were lateralized to the left hemisphere,

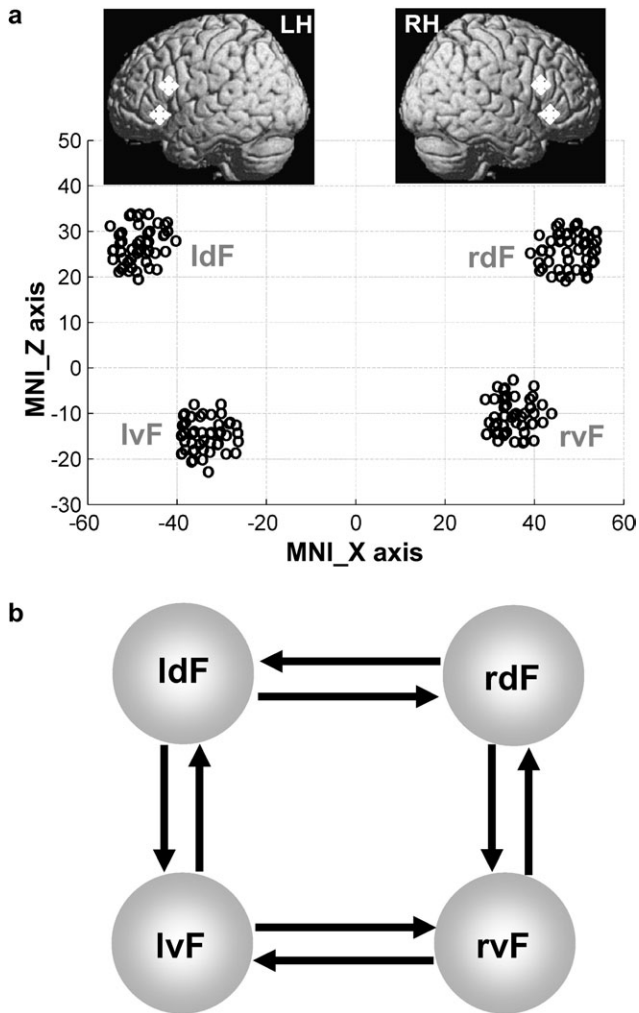


Figure 2. (a) Schematic projection of the individual coordinates of the 4 regions on a coronal view (x - z plane). The coordinates of each subject (from 1 to 60) are indicated by small circles. The mean locations of the ventral and dorsal frontal regions are shown on a 3D anatomical volume rendering. The mean (\pm SD) of the MNI coordinates of the 4 frontal regions are as follows: lvF = [$x = -36 \pm 4, y = 31 \pm 3, z = -14 \pm 3$], IdF = [$x = -50 \pm 4, y = 19 \pm 4, z = 27 \pm 4$], rvF = [$x = 34 \pm 3, y = 34 \pm 4, z = -10 \pm 4$], and rdF = [$x = 47 \pm 4, y = 20 \pm 4, z = 26 \pm 4$]. (b) Schematic view of the connectivity model with 4 regions and 8 intra- and interhemispheric endogenous connections.

across all 60 subjects, was higher when the stimuli were words than pictures (see also Supplementary Fig. 1). This illustrates that lateralization to the left hemisphere is increased for verbal relative to nonverbal stimuli ($t = 4.7$; $P < 0.001$; Fig. 1b) even when the task instructions and concept are held constant.

Within the frontal lobe, a systematic analysis of the regions activated for semantic matching on words and pictures (see Table 1) suggested that increased lateralization for words relative to pictures (Fig. 1b) was driven by greater activation for pictures in the right ventral and dorsal inferior frontal regions rather than greater activation for words in the left hemisphere homologues (Table 1, right-hand column). This unexpected finding might be explained by differences in the interhemispheric coupling between homologous frontal regions during word versus picture processing. The DCM analyses below therefore examined the relationship between lateralization and interhemispheric connectivity and determined whether this relationship differed for words and pictures.

Table 1

Regions activated by semantic matching for both words and pictures relative to perceptual matching on unfamiliar stimuli ($P < 0.05$ FWE corrected)

Contrast	(SW and SP) > PM				SW > PM	SP > PM	SW vs. SP
	Coordinates				Z-score	Z-score	Z-score
Region	x	y	z	Z-score	Z-score	Z-score	Z-score
Left ventral IFG	-34	32	-14	Inf	Inf	Inf	ns
	-42	26	-14	Inf			
	-52	30	-2	Inf			
	-44	48	-8	6.7			
Right ventral IFG	34	34	-12	7.0	4.6	7.3	-4.6
Left dorsal IFG	-50	16	28	Inf	7.7	7.7	ns
	-44	28	16	Inf			
	-54	28	18	Inf			
	-52	14	18	7.6			
Right dorsal IFG	44	20	26	6.8	5.4	6.8	-3.1
	54	22	30	5.8			
	46	32	10	6.3			
	-48	-48	-14	Inf	6.1	Inf	ns
Left middle/superior temporal gyrus	-54	-38	2	Inf			
	-60	-44	-8	6.9			
	-30	-66	42	Inf	6.4	7.3	-3.6
Left angular gyrus	-48	-68	22	6.4			
	10	-82	-34	Inf	Inf	Inf	ns
	28	-74	-44	Inf			
Right cerebellum	40	-72	-38	7.8			
	-2	14	52	Inf	Inf	7.8	ns
	-2	36	44	7.1			
Left inferior temporal cortex	-36	-40	-20	6.9	4.8	7.6	-5.0
	-28	-32	-22	6.1			
	-30	26	4	7.2	6.5	5.9	ns
Left insula	-36	28	0	6.2			
	32	24	-2	6.7	6.1	5.5	ns
	44	24	-6	5.9			
Right insula	-14	-14	12	6.7	6.0	5.6	ns
	-8	-16	8	6.6			

Note: Within each of the identified regions, we also report the effect of semantic more than perceptual matching for words and pictures independently and for the direct contrast between semantic decisions on words and pictures. Regions included in our connectivity analysis (and their coordinates) are shown in bold. SW = semantic matching on written words; SP = semantic matching on pictures of objects; PM = perceptual matching on unfamiliar stimuli. Negative values = SP > SW; ns = not significant at $P < 0.001$ uncorrected; Inf = $Z > 8.0$; IFG = inferior frontal gyrus; FWE = familywise error.

DCM analyses

DCM Parameters Estimation

DCM characterizes task-dependent neuronal interactions between regions. The starting point is the selection of a fixed set of regions and their possible connections. Each combination of experimentally modulated connections corresponds to a model, which can then be compared with all other models in order to identify which model best predicts the data. In our case, we wanted to establish which pattern of connectivity best described the interhemispheric interactions between the left and right dorsal and ventral frontal regions that were activated during semantic matching tasks. We also wanted to determine whether the best model for verbal stimuli was also the best model for nonverbal stimuli; see below the construction of our DCM model space.

All DCM analyses were carried out using the recent version of SPM8. More details about DCM can be found elsewhere (e.g., Friston et al. 2003). Briefly, for a given model, DCM estimates 3 different sets of parameters: 1) input or extrinsic parameters that quantify how brain regions respond to external stimuli (in this case, all semantically meaningful triads presented visually, irrespective of modality), 2) endogenous parameters reflecting the latent connectivity that characterizes the

context-independent coupling between regions, and 3) modulatory parameters that measure changes in effective connectivity induced by some experimental conditions. In this case, we independently investigated the modulatory effects of both types of meaningful triads on connections: words or pictures. These different parameters are expressed in hertz within the DCM framework. It is important to keep in mind that 1) DCM is not an exploratory method because it is a generic approach designed to estimate and test explicit models; 2) parameters (endogenous and modulatory) are estimated at the neuronal level; 3) the coupling between ROIs is not necessarily constrained by monosynaptic or direct anatomical connections; and 4) the estimated model is context dependent, which means that interactions and coupling among regions are constrained by the user-specified driving and modulatory inputs. All parameters (endogenous and modulatory) of the DCM model and their posterior probabilities were then assessed with Bayesian inversion by means of expectation-maximization algorithm (Friston et al. 2003).

As mentioned above, the main advantage of DCM is the opportunity to infer mechanisms at the neuronal level that provides a more precise estimation of how the rate of change of activity in one region influences the rate of change in other regions, thanks to its biophysical forward model of hemodynamic responses (Friston et al. 2003; Friston 2009). However, during the interpretation of these neuronal parameters, it is important to keep in mind the following conceptual issues: 1) due to the limited temporal resolution in fMRI, conduction delays in inputs and interregional interactions are ignored in DCM of fMRI responses (Friston et al. 2003) and thus cannot be assessed in particular when characterizing the serial information transfer and synchronization between brain areas; 2) due to the limited number of nodes that can be included in a typical deterministic DCM, indirect influences (i.e., nonmodeled effects of an area outside our 4 frontal regions) cannot be ruled out, for instance, when a connection excites a group of neurons that inhibit another region and thus results in an overall effect of inhibition; and (iii) because each region is modeled by one neuronal state equation only (see eq. 2 in Friston et al. 2003), it is not possible to assess selective changes in excitatory (glutamatergic) and inhibitory (γ -aminobutyric acidergic [GABAergic]) subpopulations in each region of the DCM model (but see Marreiros et al. 2008).

The DCM Model Space

Because the exact mechanisms behind the differential responses that we observed here are unknown, it was not possible to have an a priori prediction about the exact (i.e., true) model. Therefore, it was important to specify a range of alternative models and then search for the best model in the model space (e.g., Leff et al. 2008; Seghier and Price 2010). This procedure would increase our certainty of the best model by testing many other potential explanations of the data. To keep a reasonable size for the model space, we placed constraints on the possible circuitry of plausible DCM models. First, we limited the interhemispheric connections to the dominant homotopic connections between the frontal regions (e.g., via the genu and rostrum of the corpus callosum; Catani and Thiebaut de Schotten 2008; Park et al. 2008, see also Stark et al. 2008), thus omitting 4 diagonal (heterotopic) connections (as illustrated in Fig. 2b). Second, we excluded all models that may

artificially create an asymmetry in information flow between the 2 hemispheres, by forcing the driving inputs to enter both hemispheres simultaneously either at ventral or at dorsal frontal regions and by defining symmetrical intrahemispheric connectivity. Accordingly, all competing models have the same circuitry with 4 endogenous connections that modeled the forward and backward connections interhemispherically and another 4 that modeled the intrahemispheric connections between homologous ventral and dorsal regions. These constraints ensured that each frontal region of our DCM model was connected with the same number of inter- and intrahemispheric connections (see Fig. 2b).

The differences between competing models are expressed by 3 factors: 1) the site of the driving regions or where the inputs enter the model, 2) the site of the modulatory effect on intrahemispheric connections, and 3) the site of the modulatory effect on interhemispheric connections. In all models, the modulatory context was either word or picture triads. Practically, we first generated 15 models that represented all possible ways of modulating the interhemispheric connections between the 4 regions (noted Model 1 to Model 15, Fig. 3). These models varied from a DCM with only 1 modulated connection (e.g., Model 1) to a DCM with all 4 interhemispheric connections modulated (e.g., Model 15). Second, these 15 models were repeated or multiplied across 6 different configurations (i.e., family of models, noted A to F) that varied in terms of both their intrahemispheric modulations (3 permutations) and their driving inputs into paired regions, dorsal or ventral (Fig. 3; for a similar procedure see Penny et al. 2010). This produced 90 models per subject. The modulatory context for each of these models was explored separately for both word and picture stimuli, resulting in a total of 180 models being generated for each subject.

Random-effects BMS

For each subject, all 180 models had the same endogenous connections but differed in where modulatory and driving effects were specified (Fig. 3). To select the most plausible models, we used the random-effects BMS procedure as implemented in SPM8. As measures of model evidence, we chose the more robust and sensitive criterion based on the negative free energy (see Stephan et al. 2009). This criterion points to the optimal compromise between the accuracy and complexity of a given model. It takes into account (measures) the interdependency between the estimated parameters and therefore provides a better approximation for the complexity term compared with methods that apply a fixed term for each additional parameter. Thus, by using this optimal criterion of the negative free energy, we ensured here that 1) model complexity will not increase if additional parameters are “redundant” to existing parameters and 2) the parameter estimates of a good model are as precise and uncorrelated as possible (Stephan et al. 2009).

After estimating all models and their evidence (the negative free energy expressed here as a log-evidence), we computed the group evidence (of 90 models over 60 subjects) separately for word or picture modulation using the BMS procedure. To ensure that the BMS at the group level was not adversely affected by outliers, we used a hierarchical Bayesian approach that is robust to these effects (Stephan et al. 2009). This random-effects BMS approach quantifies, in the context of a group of subjects, how likely it is that a specific model

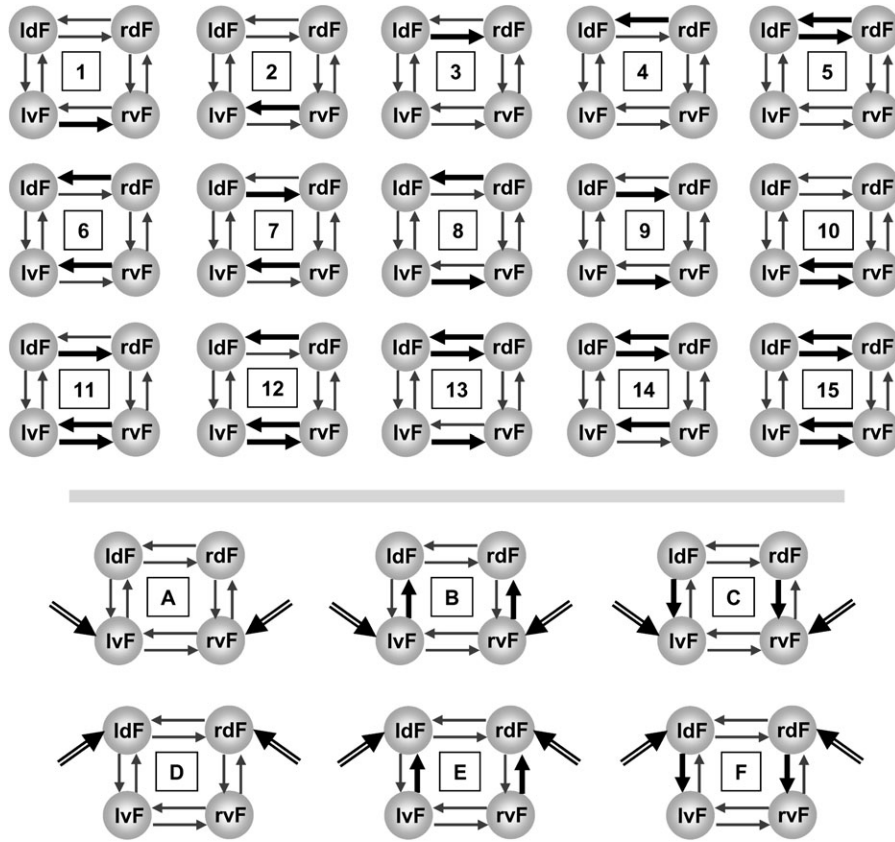


Figure 3. Illustration of the 90 different models estimated and compared here (Models 1–15 differ in interhemispheric modulations; configurations/families A to F differ in intrahemispheric modulations and driving regions). All models have the same endogenous connections. Modulated connections (by either word semantics or picture semantics) are shown with thicker arrows. Driving inputs (A–F) are shown with stripped arrows.

generated the data of a subject chosen at random (from our 60 subjects). Here, we computed 2 measures for the group evidence of a given model (Stephan et al. 2009): 1) the Dirichlet parameter estimates (alpha) as a representative measure of the effective number of subjects in which a given model generated the observed data, and 2) the “exceedance” probability (xp) that describes the belief that a particular model is more likely than any other model given the group data. Note, however, that these measures (i.e., alpha and xp) are not “absolute” for a particular model as their values depend on the relative preference/occurrence within the selected models. Although both measures are comparable when ranking models at the group level, we preferred to use exceedance probability (xp) because it is particularly intuitive (i.e., all exceedance probabilities sum to 1 over all tested models).

BMS at the Family Level and Bayesian Model Averaging

Across our 60 subjects, a random-effect BMS analysis over the whole model space (Fig. 4a) indicated that no model had an overwhelming posterior evidence compared with the rest of the models (i.e., exceedance probability $x_p < 90\%$). As illustrated in Figure 4a, the model evidence is “diluted” over our large number of models, especially when many connections were shared between models (see Fig. 3). In this situation, a recent extension of BMS has enabled inferences to be made on “families” of models (Penny et al. 2010). Here, we have defined 6 families (noted “A” to “F” in Fig. 3, see above) that partitioned the whole model space into different families with

no overlap. BMS was then used to compare these competing families so that inferences could be made at the family level. In brief, random-effect BMS at the family level uses a Gibbs sampling method to draw samples from the posterior density, where the family probabilities are given by computing the frequency of each family of models in the population and defining a prior over these probabilities using a Dirichlet density (eq. 22 in Penny et al. 2010). Then, an exceedance probability “xp” is computed (eq. 25 in Penny et al. 2010) corresponding to the belief that a particular family is more likely than any other, given the data from all subjects. In other words, xp values represent the evidence of each family of models rather than the evidence of each individual model. To make inferences on connectivity parameters, Bayesian model averaging (BMA) is then applied over the winning families. BMA can assess the full posterior density on parameters, where the contribution of each model to the mean effect is weighted by its evidence (Penny et al. 2010). Therefore, models with the highest evidence make the largest contribution, while the contribution of models with weak evidence is minimized. This model averaging can be restricted within each subject, which can be used to generate within-subject densities that can be used to compute posterior means of connectivity parameters for each subject.

The significance of the each connectivity parameter (endogenous or modulatory) is assessed by the fraction of samples in the posterior density that are different from zero (posterior densities are sampled with 10 000 data points). The

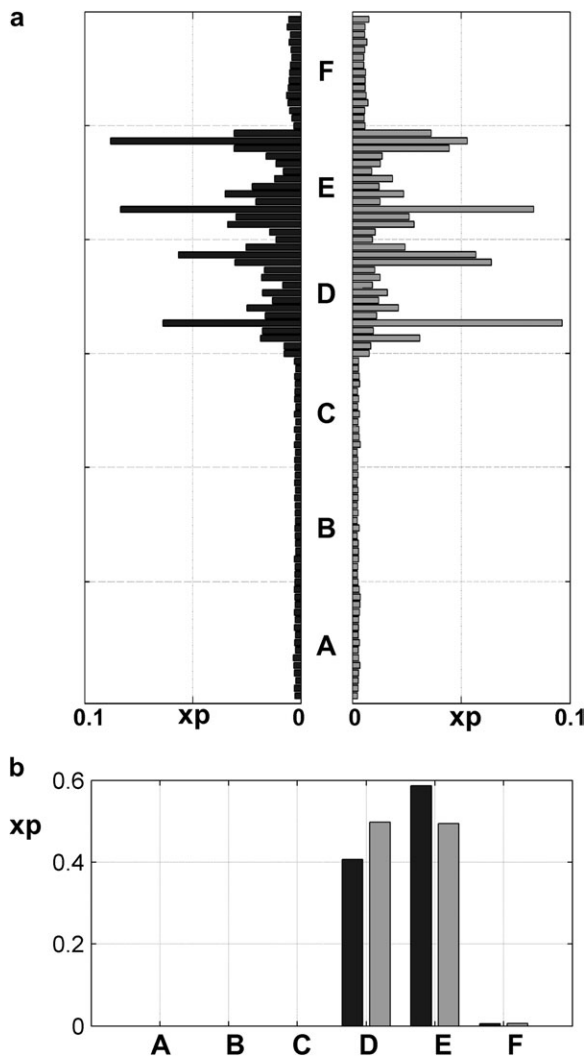


Figure 4. (a) Group random-effect BMS over the whole DCM space (90 models: Model 1–15 in families A to F). The bar graph plots the exceedance probability (xp, horizontal axis) for all models (vertical axis), when the modulatory factor is words (left, black bars) or pictures (right, gray bars). (b) Illustrates the group BMS results at the family level. The bar graph plots the exceedance probability (xp) for families A to F when the modulatory factor is words (black bars) or pictures (gray bars). Each family contains a set of 15 models as shown in Figure 3. Families D and E have higher evidence than the remaining families.

difference in modulatory effects for words versus pictures is assessed by the fraction of samples that are higher in words than pictures. Significant effects are reported at a posterior probability threshold of 0.95. The posterior means of connectivity parameters were also submitted to the following analyses: 1) across-subject correlations between connectivity parameters and laterality indices and their interactions with words/pictures; and 2) correlations between connectivity parameters and handedness, age, gender and response times.

Results

Behavioral Results

Accuracy across sessions was on average $92 \pm 8\%$ and $91 \pm 8\%$ for matching words and pictures, respectively. The reaction times (RTs) were 1715 ± 290 ms and 1780 ± 280 ms for words

and pictures, respectively, with a trend for slightly slower RTs (difference of 65 ms in average) for pictures compared with words ($t = 2.2$, $P = 0.03$). However, after controlling for visuomotor processing by subtracting each semantic matching condition to its respective perceptual matching baseline, RTs for semantic matching were similar for both words and pictures (i.e., RTs matching words minus RTs perceptual matching on unfamiliar symbols = 590 ± 277 ms; RTs matching pictures minus RTs perceptual matching on unfamiliar non-objects = 610 ± 230 ms; difference not significant: $t = 0.66$, $P > 0.1$).

DCM Results

Below, we present the findings from our DCM analyses with the following step-by-step approach. First, the winning configurations or families (A to F, Fig. 3) across all subjects were identified using the random-effects BMS at the family level in order to reveal the optimal input regions and intrahemispheric modulations. Second, connectivity parameters densities were assessed with BMA within the winning families, and their posterior means and probabilities were then reported at the group and the individual level.

The Winning Families with BMS

We compared the 6 different configurations/families (A to F) using the BMS approach to reveal the optimal configuration of input regions and intrahemispheric modulations for words and pictures (Fig. 4b). When the modulatory factor was words, the winning families were family E ($xp = 0.587$) and D ($xp = 0.407$), which means that families E and D accounted for a total of 0.994 in exceedance probability (for a similar procedure see Penny et al. 2010). In both families E and D, the driving inputs were to the dorsal rather than ventral frontal regions. In addition, evidence for E suggests that words increased the intrahemisphere connectivity (feedback) from the ventral to the dorsal frontal regions. Likewise, when the modulatory factor was pictures, configurations E ($xp = 0.495$) and D ($xp = 0.499$) were the best explanation of the data with a total exceedance probability of 0.993 (see Fig. 4b). To summarize, our BMS results at the family level over 60 subjects show that, irrespective of modality, 1) the driving inputs entered at the left and right dorsal frontal regions, and 2) intrahemispheric modulations were either absent or from ventral to dorsal frontal regions.

The Significant Connectivity Parameters with BMA

Endogenous connectivity. BMA, within the 2 winning families and across our 60 subjects, showed that all the endogenous/latent connectivity parameters were significant (posterior probabilities > 0.95) and positive with values ranging from 0.07 to 0.23 Hz (see Table 2). These values represent the latent (i.e., fixed or average) effective connectivity in our DCM model that is present in the system irrespective of the modulatory factor. Their positivity indicates that activity changes in one region increased with activity in other regions.

Modulatory effects for words and pictures. The only significant modulatory effects (BMA across our 60 subjects at $P > 0.95$) for both words and pictures were on the lDF to rDF connection. As illustrated in Figure 5, this significant modulation was negative for words (-0.034 Hz) and positive for

pictures (+0.043 Hz), which indicates that information flow to rdF was decreased (by 22%) when the stimuli were words. These effects differed significantly for words versus pictures on the ldF to rdF connection (i.e., modulation strength significantly lower for words than pictures, $P < 0.0007$). This significant decrease in connectivity for words mirrors the increase in laterality illustrated in Figure 1b. There were no significant differences between word and picture modulations on any other connections (see Fig. 5).

Explaining Left Lateralization for Language

We searched for any significant correlations between individual laterality indices and the connectivity parameters. First, the endogenous connectivity (Table 2), representing the connectivity that is present in the system irrespective of inputs, showed significant correlations with laterality. Specifically, the strength of intrahemispheric connections in the right hemisphere was negatively correlated with laterality indices

Table 2

Mean of endogenous connections (in hertz) at the group level from the BMA analysis (all significant at $P > 0.95$)

		From (out)			
		lvF	ldF	rvF	rdF
To (in)	lvF	—	0.23	0.07	—
	ldF	0.10	—	—	0.15
	rvF	0.09	—	—	0.20
	rdF	—	0.15	0.07	—

for words (rvF to rdF: $r = -0.29$, $P = 0.02$; rdF to rvF: $r = -0.31$, $P = 0.01$) and pictures (rvF to rdF: $r = -0.36$, $P = 0.005$; rdF to rvF: $r = -0.40$, $P = 0.002$). In addition, laterality for words was positively correlated with endogenous connectivity from ldF to lvF ($r = 0.32$, $P = 0.01$), and laterality for pictures was negatively correlated with connectivity from rvF to lvF ($r = -0.28$, $P = 0.03$). This suggests that strong left-lateralized activations for words and pictures emerged when endogenous interactions 1) decreased between right hemisphere regions, 2) increased between left regions, or 3) decreased from right to left ventral frontal region.

Correlations between individual laterality indices and the modulatory connectivity parameters demonstrated that the increase in laterality for words versus pictures (Fig. 1b) can be explained by decreased interhemispheric interactions when the modulatory factor was words (e.g., see Fig. 5). More specifically, we found that left lateralization for word processing was higher when information flow from lvF to rdF decreased ($r = -0.33$, $P = 0.01$, Fig. 6). For pictures, this correlation was not significant ($r = 0.23$, $P > 0.05$). Consequently, the negative correlation between laterality indices and modulatory effects was stronger for words than pictures on the ldF to rdF connection ($P < 0.002$, using Fisher's transform).

In contrast to the significant negative correlations between lateralization and information flow from ldF to rdF (Fig. 6), there were no significant correlation ($P > 0.05$) with lateralization on the connection from rdF to ldF (for words: $r = -0.02$; for pictures: $r = 0.18$), from lvF to rvF (for words: $r = 0.22$; for pictures: $r = -0.07$), from rvF to lvF (for words: $r = -0.03$; for

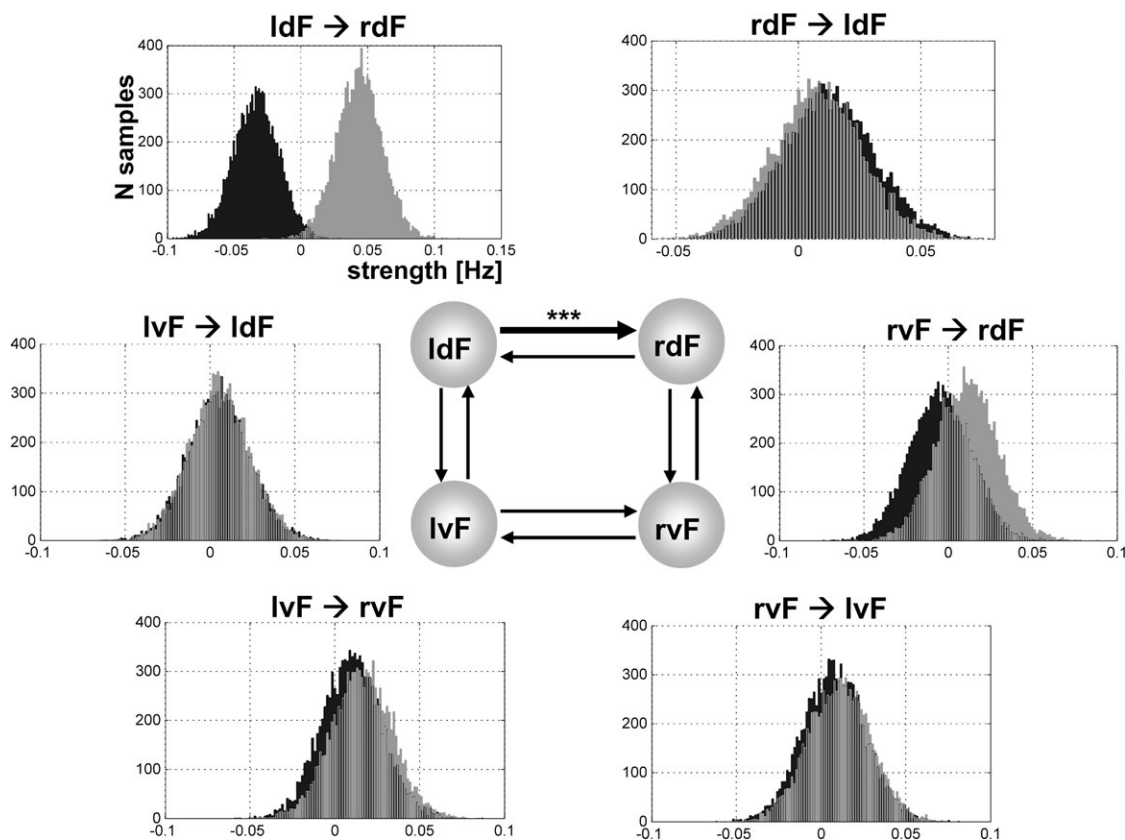


Figure 5. Illustration of the group BMA results of the modulatory effects over the 2 winning families D and E. For each connection, the distribution of the 10 000 samples of the posterior densities is provided for words (black) and pictures (gray). The connection where the modulatory effects were significant is indicated by 3 asterisks (connection ldF to rdF).

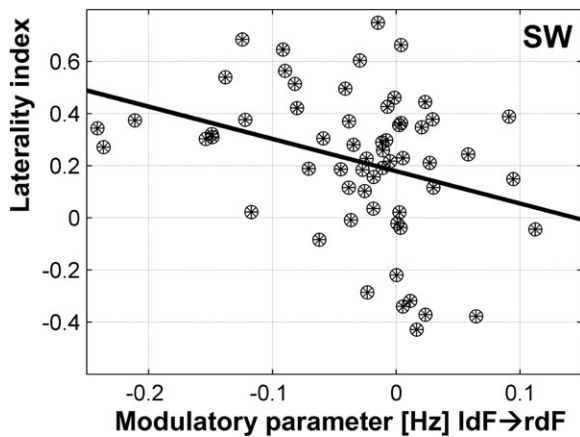


Figure 6. Illustration of the significant correlation between the LI and the modulatory parameters for words ($r = -0.33$, $P = 0.01$) on the interhemispheric connection IdF to rdF. Each data point represents 1 subject.

pictures: $r = -0.19$), from lvF to ldF (for words: $r = 0.11$; for pictures: $r = 0.05$), or from rvF to rdF (for words: $r = -0.19$; for pictures: $r = -0.04$).

In summary, across 60 subjects, increased left-lateralization was negatively correlated with interhemispheric modulations from ldF to rdF for words but not pictures. This suggests that left hemisphere dominance is predicted by information flow from the left dorsal frontal (ldF) to the right dorsal frontal cortex (rdF), with greater lateralization when there is reduced interhemispheric coupling.

Effective Connectivity and Other Variables

We also investigated whether interregional interactions were related to handedness, gender, age, and/or response times. Right-handers had higher word modulations than left-handers on the intrahemispheric connection between lvF and ldF ($t = 2.8$, $P = 0.007$) while left-handers had stronger picture modulations than right-handers on the connection from rvF to lvF ($t = 2.9$, $P = 0.006$). There were no significant correlations between effective connectivity and age, gender, or response times. The latter suggests that “difficulty” cannot explain the effective connectivity modulations that were observed for words and pictures.

Discussion

Our results demonstrate for the first time that intersubject variability in left hemisphere lateralization for verbal (words) relative to nonverbal (pictures) stimuli correlates with information transfer from the left to the right hemisphere even when the task (semantic matching) and concept (objects) are carefully controlled. Our discussion is centered around a hierarchical series of questions. First, we discuss the evidence for driving inputs entering our DCM models at dorsal frontal regions and the intrahemispheric modulatory effects for words and pictures on the connection from ventral to dorsal frontal regions. Second, we consider the evidence for interhemispheric interactions by asking how the left and right frontal regions interact with one another during our semantic matching task. Third, we consider 4 unexpected results related to increased lateralization for verbal relative to nonverbal stimuli. Finally, we discuss the multiple mechanisms that contribute to lateralized brain function (for a review see

Banich and Belger 1990; Cook and Beech 1990; Chiarello and Maxfield 1996; Stephan, Fink et al. 2007; Belin et al. 2008).

Driving Regions and Intrahemispheric Interactions

DCM models with inputs to dorsal frontal regions had greater evidence than the same models with inputs to ventral frontal regions (e.g., families D and E better than A, B, and C; see Fig. 4b). This suggests that semantic matching activation for both word and picture triads drives connectivity in our DCM model (Fig. 2b) in the dorsal rather than ventral parts of the inferior frontal gyrus. This unexpected result is supported by 2 recent studies that showed a significant relationship between language lateralization and anatomical connectivity (i.e., the size of the corpus callosum) in dorsal frontal regions located very close to our ROI at [$x = -44$, $y = 10$, $z = 20$] (Josse et al. 2008) or [$x = -53$, $y = 16$, $z = 24$] (Putnam et al. 2008). Regarding the intrahemispheric interactions, we found that the best intrahemispheric modulations (e.g., family E had higher evidence than family F, see Fig. 4b) were on the feedback connection from ventral to dorsal frontal for both words and pictures. However, this effect was not significant in the group BMA analysis, which may explain why there was also high evidence for family D that had no intrahemispheric modulations (see Figs 4 and 5).

Interhemispheric Modulations (Differences between Verbal and Nonverbal Stimuli)

The critical observation here is that increased left lateralization for verbal (words) relative to nonverbal (pictures) stimuli (Fig. 1b) was associated with a 22% decrease in coupling from left to right dorsal frontal region for words but not pictures (Figs 5 and 6). As there was no effect of stimulus modality on the opposite connection, the effective connectivity from left to right dorsal frontal regions decreased for words compared with pictures. This suggests that left lateralization is greater when less information is passed from the left to the right hemisphere. Consistent with this conclusion, we found a significant and negative correlation between laterality indices for words and effective connectivity from ldF to rdF (Fig. 6). Thus, participants with strongly left lateralized semantic activation for words had weaker interactions from ldF to rdF, whereas participants with weak laterality for words had stronger interactions from ldF to rdF. Regarding the exact nature of such interactions, it is unclear whether the interhemispheric information transfer via the corpus callosum between homologous areas such as ldF and rdF is mainly excitatory or inhibitory (Bloom and Hynd 2005). Mechanistically, both weaker excitatory or stronger inhibitory effects may result in a decrease in interhemispheric coupling, but we turn here to previous work that has suggested that callosal inhibition mechanisms dominate the interactions between homotopic regions during the processing of lateralized functions (e.g., Cook 1984; Karbe et al. 1998).

Four Unexpected Results for Word versus Picture Activation

Four unexpected findings were obtained. First, greater lateralization for words than pictures resulted from greater activation for pictures in the right ventral and dorsal inferior frontal regions rather than greater activation for words in the left

hemisphere homologues (see Table 1). Thus, increased left lateralization for words in the inferior frontal cortex could not simply be explained by greater phonological processing of words (Nelson and Castano 1984; Glaser WR and Glaser MO 1989) in our left frontal regions.

A second unexpected finding was that the laterality effect for words is more related to the unidirectional coupling from left to right and not the reverse. When interhemispheric cooperation occurred, we would expect that a decrease in information flow from the left to the right hemisphere would result in less feedback from the right to the left hemisphere, but this was not evident in our data (e.g., Fig. 5). Instead, our findings are more consistent with unidirectional interhemispheric suppression of information flow from the left to the right hemisphere (Moscovitch 1976; Hutner and Liederman 1991) that can be sufficient to magnify hemispheric asymmetry for verbal stimuli (for a detailed discussion see Chiarello and Maxfield 1996). Unidirectional suppression has previously been observed with DCM in other contexts, including the connectivity between striatal-thalamic and frontoparietal networks during response inhibition of a go/no-go task (Stevens et al. 2007) and during the suppression of ipsilateral hemisphere activity during the coordination of unilateral hand movements (Grefkes et al. 2008). Although the nodes that trigger or gate this unidirectional interhemispheric suppression have not been identified, we can tentatively suggest that in our paradigm it is driven by processing that is more involved in word processing than picture processing. For instance, it is plausible that activity in left phonological processing areas (Wise et al. 1999; Crosson et al. 2003; Riecker et al. 2005; Borowsky et al. 2006), such as the supramarginal gyrus, insula, putamen, or preSMA, are involved in gating the frontal interhemispheric interactions. This hypothesis could be tested using the new extended nonlinear DCM framework (Stephan et al. 2008).

A third unexpected finding was that the modulation on interhemispheric interactions observed here cannot explain the laterality for nonverbal stimuli. In fact, our results indicated that laterality for pictures was sufficiently explained by the endogenous connectivity that is present on average in our DCM system (Table 2). This concerned the intrahemispheric connections between rvF and rdF and the interhemispheric connection from rvF to lvF. The absence of a significant link between laterality for pictures and modulatory effects requires future investigations but one possible explanation is that the interregional interactions that are related to laterality for pictures may occur on the interhemispheric connections between posterior language areas (e.g., temporal lobe structures).

A fourth unexpected finding was that, despite differences in the modulatory effects of words and pictures on the interhemispheric connections, intrahemispheric connections between ventral and dorsal frontal regions were similarly modulated by words and pictures (Fig. 5). Thus, there was no evidence for the influence of phonological processing on these connections during semantic word matching. We consider 2 possible explanations. One is that the influence of phonological processing during word processing might have been more evident if our DCM analyses included data from other frontal regions, for instance, the premotor cortex where our previous DCM study (Mechelli et al. 2005) reported higher modulation between the left premotor cortex and the left posterior fusiform gyrus for pseudoword reading (that relies on

phonological mediation) compared with reading irregularly spelled words (that relies on lexical or semantic mediation). The other possible explanation is that phonological processing may have had stronger effects on connectivity if different tasks were included. For instance, Heim et al. (2009) found that, phonological relative to semantic fluency had a greater modulatory effect on the interactions between BA 44, BA 45, and the motor region M1. Note, however, that all previous DCM studies on frontal regions have restricted their models within the left hemisphere, whereas our DCM models allowed the influence from homotopic right frontal regions to be expressed and thus quantified.

Laterality: Multiple Mechanisms

There is converging evidence that lateralized hemispheric function enhances brain efficiency in different cognitive tasks (e.g., Rogers et al. 2004; Belin et al. 2008), although the exact mechanisms behind the emergence of such lateralized patterns are still unknown (Beaumont 1997; Banich and Weissman 2000). We briefly consider 3 possible hypotheses that may explain the lateralized patterns we observed here. The first hypothesis assumes that functional laterality is inherent to structural asymmetries in the brain (e.g., Galaburda et al. 1978; Watkins et al. 2001; Barrick et al. 2007). For instance, we have recently shown that individual laterality indices are significantly related to the size of the corpus callosum (Josse et al. 2008) and asymmetry in gray matter density (Josse et al. 2009). However, structural asymmetries cannot fully explain the dynamic context-dependent nature of functional laterality (e.g., see Discussion in Wada 2009) when anatomy is held constant (e.g., the within-subject changes in laterality that we observed for words and pictures; Fig. 1*b*).

The second hypothesis attributes asymmetrical activation patterns to differences in the functional properties of each hemisphere. For instance, previous work has suggested that the left and right hemispheres play different roles during the categorization and semantic processing for words and pictures (e.g., see Koivisto and Laine 2000; Koivisto and Revonsuo 2000), with words increasing left hemisphere verbal, analytical, and high-frequency processing and pictures increasing visuo-spatial, configurative and low-frequency processing (for review see Dien 2009). These models may partly explain why we found higher right hemisphere activation for pictures than words (Table 1) even when concept and task were held constant.

The third hypothesis, and probably the most important one, is that laterality is regulated by the dynamic flow of interhemispheric interactions (Bryden and Bulman-Fleming 1994; Chiarello and Maxfield 1996; Belin et al. 2008), as we have shown here with DCM. For instance, all endogenous interhemispheric interactions between left and right frontal regions were consistently significant across all subjects (Table 2), suggesting strong interhemispheric cooperation/collaboration (Bloom and Hynd 2005) during semantic matching. This endogenous connectivity was significantly related to laterality indices for both words and pictures, as discussed above. Furthermore, the additional decrease in interhemispheric interactions from ldF to rdF for words (i.e., modulatory effects) was correlated with the increase in laterality during words compared with pictures. This again stresses the dominant contribution of interhemispheric interactions in the emergence of lateralized semantic activation.

Conclusion

In summary, using DCM analysis, random-effects BMS, and averaging (BMA) in 60 healthy subjects, we demonstrate for the first time that 1) increased left lateralization for verbal compared with nonverbal stimuli is a reflection of less right hemisphere activation rather than more left hemisphere activation and 2) this is a consequence of reduced information flow from the left to the right hemisphere. Our results have theoretical implications for understanding how the left and right hemispheres communicate with one another. Our findings also motivate further studies that use a similar framework to investigate interhemispheric connectivity in posterior language networks (e.g., temporal areas), during other language tasks (e.g., phonologic and syntactic) and modalities (visual vs. auditory), during development and learning (e.g., age, multilingualism), and following brain damage (Sonty et al. 2007; Abutalebi et al. 2009).

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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