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Negation in the brain: Modulating action representations

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ABSTRACT

Sentential negation is a universal syntactic feature of human languages that reverses the truth value expressed by a sentence. An intriguing question concerns what brain mechanisms underlie our ability to represent and understand the meaning of negative sentences. We approach this issue by investigating action-related language processing and the associated neural representations. Using functional magnetic resonance imaging we measured brain activity in 18 healthy subjects during passive listening of sentences characterized by a factorial combination of polarity (affirmative vs. negative) and concreteness (action-related vs. abstract). Negation deactivated cortical areas and the left pallidum. Compared to abstract sentences, action-related sentences activated the left-hemispheric action-representation system. Crucially, the polarity by concreteness interactions showed that the activity within the action-representation system was specifically reduced for negative action-related vs. affirmative action-related sentences (compared to abstract sentences). Accordingly, functional integration within this system as measured by Dynamic Causal Modeling was specifically weaker for negative action-related than for affirmative action-related sentences. This modulation of action representations indicates that sentential negation transiently reduces the access to mental representations of the negated information.

Introduction

Sentential negation is a universal syntactic feature of human languages that mediates the expression of the reverse truth value of any given sentence. Across languages it is invariably grammaticalized by using lexical morphemes, such as “not” in “John has not left” vs. “John has left” (Horn, 1989; Zanuttini, 1997). In other words, in no language can a negative sentence be realized by simply rearranging the word order of the corresponding affirmative declarative sentence. This sharply contrasts with cases like interrogative sentences, such as “Has John left?” derived from its affirmative counterpart “John has left”. Abundant psycholinguistic research has been devoted in the past to investigate how sentential negation affects language processing. Two main classes of results have emerged from these studies. On the one hand, sentence comprehension – as tested for example in sentence-picture matching tasks (Carpenter and Just, 1975; Clark and Chase, 1972; Trabasso et al., 1971) – was shown to be more difficult for negative than for affirmative sentences. Negative sentences required longer processing times and were associated with higher error rates. On the other hand, studies testing for the impact of negation on the accessibility of information mentioned within its scope – using for instance word recognition or priming tasks (MacDonald and Just, 1989; Kaup, 2001; Kaup and Zwaan, 2003) – showed that response times were significantly longer for negated than for non-negated items. These two classes of evidence have led to divergent views on the mental representation of negation. The first type of evidence has been taken to suggest that negative sentences are syntactically more demanding than affirmative sentences, and according to this view stronger activations of perisylvian brain regions are to be expected. In turn, the second type of evidence speaks for a reduced access to conceptual representations of the negated items; accordingly, reduced activations of the brain circuits involved in conceptual representations are to be expected.

The neural correlates underlying the processing of syntactic negation are still largely unknown. Two different fMRI studies have tested the hypothesis of a higher computational load for negative compared to affirmative sentences. In one study, negative vs. affirmative sentences describing visuo-spatial relations were compared. Significantly higher activations in the left posterior temporal and bilateral posterior parietal lobes were found for negative sentences (Carpenter et al., 1999). In the second study on bilingual subjects, higher signal for negation vs. affirmation was found in left

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perisylvian regions, but only in the participants' second language, which was mastered at a moderate level of proficiency, and not in their first language (Hasegawa et al., 2002). Altogether, it seems that negation elicited higher activations only in combination with increased extrinsic, non-linguistic task demands, such as the processing of visuo-spatial relations or of a second language at low proficiency.

An important unresolved question regards whether the impact of negation on the neural responses elicited by the negated propositions is dependent or independent from the semantic field involved. For example – based on the evidence of partially segregated anatomo-functional correlates for concrete vs. abstract semantic contents (Binder et al., 2005; Kiehl et al., 1999; Martin-Loeches et al., 2001; Perani et al., 1999; Sabsevitz et al., 2005; Tyler et al., 2001) – if negation determines a reduced access to the mental representations of negated concepts, anatomically distinct modulatory effects for concrete or abstract semantic content should be expected. The present experiment addresses precisely this issue, hinging on language simulation theories, which postulate that language comprehension is mediated by implicit sensorimotor simulations of the content described by linguistic utterances (Barsalou, 1999; Glenberg and Kaschak, 2002). Mental simulation mechanisms have been specifically implicated with respect to the role of the action-representation system in embodied language representations (Gallese, 2007), with mirror neurons providing a plausible neurophysiological substrate (Rizzolatti and Craighero, 2004). A growing number of studies has consistently shown that linguistic utterances describing actions performed by different body parts activate the same action-representation circuits which subserve the execution and the observation of the actions described (Pulvermuller, 2005). Somatotopically organized effects in the left premotor cortex have been found with fMRI for mouth-, hand-, and leg-related verbs (Hauk et al., 2004), phrases (Aziz-Zadeh et al., 2006), and sentences (Tettamanti et al., 2005). In the latter study, activations for action-related sentences compared to abstract sentences were not confined to the left premotor cortex, but extended into the entire left fronto-parieto-temporal system subserving action representation, including the inferior parietal lobule and the posterior temporal cortex. In turn, abstract sentences compared to action-related sentences were specifically associated with an effect in the posterior cingulate cortex.

If negation indeed determines a reduced access to the specific semantic information contained in the predicate of the negated propositions, we should expect two distinct effects: 1) a reduced haemodynamic response in the left fronto-parieto-temporal system representing actions for negative vs. affirmative action-related sentences; and 2) a reduced response in the posterior cingulate cortex for negative vs. affirmative abstract sentences. As a consequence of the content-specific activation reduction, we should also expect that the functional integration between the brain regions constituting the left fronto-parieto-temporal system as measured by effective connectivity (Lee et al., 2006) are reduced in the context of negative action-related sentences. In other words, we should expect a stronger, synergistic increase of activity in the brain regions constituting the action-representation system for affirmative vs. negative action-related sentences. Conversely, if negation is associated with higher syntactic computational loads, we should expect stronger, content-independent regional haemodynamic responses for negative vs. affirmative sentences, possibly in left perisylvian areas.

In an event-related fMRI experiment, 18 participants passively listened to declarative sentences (Supplementary Table 1) characterized by the factorial combination of polarity (affirmation or negation) and concreteness (action-related or abstract). Based on this factorial design, we addressed two independent issues: the anatomo-functional correlates of sentential negation, and the interaction between polarity and concreteness. We assessed both functional specialization, under classical General Linear Model assumptions, and functional integration, using Dynamic Causal Modeling (DCM) (Friston et al., 2003). Abstract sentences described operations in which no physical entities were involved, such as “Ora apprezzo la fedeltà” (“Now I appreciate loyalty”). Action-related sentences, instead, described actions involving physical entities, such as “Ora premo il bottone” (“Now I push the button”).

Materials and methods

Subjects

Eighteen right-handed volunteer subjects (12 females, mean age 24.7 years, range 20–34 years) of comparable education level (Graduate Level) took part in the experiment. Participants were all native monolingual speakers of Italian, with no history of neurological or psychiatric disorders and no structural brain abnormalities. They gave written consent to participate in the study after receiving an explanation of the procedures. The study was approved by the Ethics Committee of the San Raffaele Scientific Institute, Milano, Italy.

Stimuli and experimental design

The experiment consisted in a 2 × 2 factorial design, the two factors being concreteness (two levels: action-related or abstract) and polarity (two levels: affirmative or negative). An initial set of 60 action-related sentences and 60 abstract sentences was generated, reflecting the two levels of the first factor. All sentences began with an adverb followed by a transitive verb in the first person singular, and a syntactically and semantically congruent object complement. Each sentence was then repeated two times with minimal variations, reflecting the two levels of the second factor, yielding i) an affirmative sentence with subject pronoun, and ii) a negative sentence without subject pronoun. Subject pronouns were included in affirmative sentences in order to control for a potential bias inherent to the total number of words of the sentences, since negation in Italian is a single word (“non”). Notably, it is a well-known fact that in all languages sentential negation must be expressed by introducing specific lexical items. The choice for subject pronouns as opposed to other words was motivated by the fact that subject pronouns do not add extra information, since the features of number and person that the pronoun carries are already present in Italian verbal inflections. It must be reminded that in Italian as opposed to languages like English pronouns are not obligatorily expressed in the subject position.

In sum, the four experimental conditions, corresponding to the 2 × 2 factorial design were: (ActA) Action-related affirmative sentences (e.g. “Adesso io premo il bottone”, “Now I push$_{\{\text{first person singular (1ps)}\}}$ the button”); (ActN) Action-related negative sentences (e.g. “Adesso non premo il bottone”, “Now not push$_{\{1\text{ps}\}}$ the button”); (AbstA) Abstract affirmative sentences (e.g. “Ora io apprezzo la fedeltà”, “Now I appreciate$_{\{1\text{ps}\}}$ the loyalty”); (AbstN) Abstract negative sentences (e.g. “Ora non apprezzo la fedeltà”, “Now not appreciate$_{\{1\text{ps}\}}$ the loyalty”). Each experimental condition included 60 sentences (Supplementary Table 1). The initial set of 60 action-related sentences included sentences describing actions performed with the mouth (12 sentences, e.g. “Adesso mordo la mela”, “Now bite$_{\{1\text{ps}\}}$ the apple”) and with the hand (48 sentences).

The frequency of adverbs, verbs, and object complements were balanced between action-related and abstract conditions, based on the available frequency norms of Italian (De Mauro et al., 1993). We also balanced the total number of syllables for each sentence between action-related and abstract conditions. The choice of stimuli was based on a norm for comprehensibility on 20 normal adults, to avoid interference with lexical difficulty. Sentences were digitally recorded by a native Italian speaker. Average sentence length was 2293 ms (st. dev. 192 ms), (condition ActA: 2337 ms (st. dev. 187 ms); condition ActN: 2290 ms (st. dev. 192 ms); condition AbstA: 2301 ms (st. dev.

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187); condition AbstN: 2244 ms (st. dev. 193). Although sentence duration slightly differed between the 2 levels of the polarity factor (ANOVA, $P<0.03$, $F(1,59)=4.77$), there were neither a significant difference in duration between action-related and abstract sentences, nor a significant interaction between the levels of the two factors. Using SoundForge 6.0 (www.sonicfoundry.com), sentences were subsequently low pass filtered and normalized. A varying period of silence was added to the end of each sentence, so that the global stimulus duration was 4000 ms for all sentences. Subjects heard all auditory stimuli via MRI-compatible headphones connected to a personal computer. Stimuli were presented with Presentation 9.90 (Neurobehavioral Systems, Albany, CA, USA) in 9 separate sessions (26/27 stimuli each) in pseudo-randomized order, such that there were no more than three consecutive stimuli of the same condition. The number of sentences of each condition was counter-balanced across sessions. Sentences were presented in an event-related mode. Within sessions, sentences were spaced by variable interstimulus intervals corresponding to three different durations, i.e. 1873 ms, 3558 ms, and 4964 ms (randomly ordered, in the proportion 4:2:1). Intervals of varying durations were used to maximise the haemodynamic signal sensitivity of the event-related design (Dale, 1999).

MRI data acquisition

MRI scans were acquired on a 3 T Intera Philips body scanner (Philips Medical Systems, Best, NL) using an 8 channels-sense head coil (sense reduction factor = 2). Whole-brain functional images were obtained with a T2*-weighted gradient-echo, echo-planar sequence, using blood-oxygenation-level-dependent contrast. Each functional image comprised 30 contiguous axial slices (4 mm thick), acquired in interleaved mode, and with a repetition time of 2100 ms (echo time: 30 ms; field of view: 240 mm × 240 mm; matrix size: 128 × 128). Each participant underwent 9 functional scanning sessions. The duration of each session was 136 scans, preceded by 10 dummy scans that were discarded prior to data analysis.

For anatomical localization and visualization of brain activations, we acquired 2 high-resolution whole-brain structural T1 weighted scans (resolution 1 mm × 1 mm × 1 mm) of each participant. The normalized structural images of all participants were then averaged in one single image. This average structural image was automatically segmented with Caret 5.4 to obtain a cortical surface reconstruction with tissue specific image values for sulcal vs. gyral cortex (Van Essen et al., 2001). Caret 5.4 was also used to map brain activations obtained with SPM2 onto anatomical slices and cortical surface maps.

Data analysis

Statistical parametric mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) was used for slice timing, image realignment and unwarping (Andersson et al., 2001), normalization to the Montreal Neurological Institute (MNI) standard space, smoothing by a 6 mm FWHM Gaussian kernel, and General Linear Model statistical analysis (Friston et al., 2002). We adopted a two-stage random-effects approach to ensure generalizability of the results at the population level (Penny and Holmes, 2003).

First-level General Linear models

At the first stage, the time series of each participant were high-pass filtered at 67 s and pre-whitened by means of an autoregressive model AR(1) (Friston et al., 2002). No global normalization was performed. Haemodynamic evoked responses for all experimental conditions were modeled as Finite Impulse Responses (Henson, 2003), consisting in trains of 12 contiguous box-car functions of 2100 ms duration each, with the onset of each train corresponding to the onset of auditory sentence presentation. A Finite Impulse Response model was chosen to account for non-canonical sustained responses associated with the processing of the entire sentence. For each participant, we modeled a 2 × 2 factorial design with 9 separate sessions, each including conditions ActA, ActN, AbstA, AbstN, and we specified a set of first-level t-Student contrasts, each contrast including a weight of one for a particular regressor of interest and a weight of zero for all the other regressors. This resulted in one contrast per experimental condition and per post-stimulus time bin ($4 \times 12 = 48$ contrasts) for each participant.

Second-level General Linear model

At the second stage of analysis, the contrast images obtained at the single-subject level were used to compute a within-subjects one way ANOVA assessing their significance at the group-level ($n=18$ participants). The ANOVA included the set of all first-level contrast images, one image per participant, per experimental condition, and per post-stimulus time bin. The contrasts assessed at the second level included: i) action-related vs. abstract: (ActA + ActN) − (AbstA + AbstN); ii) abstract vs. action-related: (AbstA + AbstN) − (ActA + ActN); iii) affirmative vs. negative: (ActA + AbstA) − (ActN + AbstN); iv) negative vs. affirmative: (ActN + AbstN) − (ActA + AbstA); v) specific activations for action-related affirmative sentences: (ActA − ActN) − (AbstA − AbstN) inclusively masked by (ActA − ActN), vi) specific activations for action-related negative sentences: (ActN − ActA) − (AbstN − AbstA) inclusively masked by (ActN − ActA), vii) specific activations for abstract affirmative sentences: (AbstA − AbstN) − (ActA − ActN) inclusively masked by (AbstA − AbstN), and viii) specific activations for abstract negative sentences: (AbstN − AbstA) − (ActN − ActA) inclusively masked by (AbstN − AbstA).

We assessed these group-level main and interaction effects with t-Student contrasts weighted with a canonical haemodynamic response function spanning all post-stimulus time bins. All reported effects relate to voxel-level statistics ($P<0.05$, false discovery rate (FDR) error type correction). For all the contrasts listed above, we inspected the corresponding beta estimates to investigate whether the observed contrasts were driven by differences in activations or deactivations.

Small volume correction for multiple comparisons

In the current study, we wished to assess the modulatory effects of sentential negation on the neural systems activated by action-related vs. abstract sentences in our previous study (Tettamanti et al., 2005). To do so, we adopted a small volume correction for multiple comparisons ($P<0.05$, FDR corrected). The choice of the correction volumes was based on the results of the previous study: an "action-related mask", including those voxels that passed a threshold of $P<0.001$ uncorrected in the main effect action-related > abstract [(mouth + hand + leg) − abstract], was applied to contrasts i, v, and vi listed above; an "abstract-related mask", including those voxels that passed a threshold of $P<0.001$ uncorrected in the main effect abstract > action-related [abstract − (mouth + hand + leg)], was applied to contrasts ii, vii, and viii.

Dynamic Causal Modeling

A complementary approach to the investigation of brain functional specialization related to a specific task is the analysis of functional integration, by means of methods which estimate the coupling of brain areas and the influence of experimental manipulations on that coupling (Lee et al., 2006). One of these methods is Dynamic Causal Modeling (DCM), which derives connectivity parameters for the influence of the experimental conditions on brain states, for the intrinsic connections between the brain areas included in the system, and for the changes in connectivity between areas induced by the experimental conditions (Friston et al., 2003). Here we used DCM, as implemented in SPM5 (Wellcome Department of Imaging Neuroscience, London, UK), to measure how the connectivity between brain regions constituting the left-hemispheric fronto-parieto-temporal system is modulated by concreteness and by the interaction

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between concreteness and polarity. More specifically, we expected to find a more positive coupling of activity (more positive connection strengths) between the areas constituting the action-representation system for action-related vs. abstract sentences (main effect of concreteness), and also specifically for action-related affirmative sentences vs. all other sentence types (specific concreteness by polarity interaction effect for action-related affirmative sentences).

To this purpose, we specified for each participant a dynamic causal model that tested whether stimulus-bound activity in an input region activated by all experimental conditions is conveyed to brain regions constituting the left-hemispheric fronto-parieto-temporal system in a way that reflects both the main effect of concreteness and the concreteness by polarity interaction. In preparation of DCM, we first specified two first-level General Linear Model matrices that were specifically designed to encompass the DCM requirements. The first GLM matrix (dcm-GLM) was entered during DCM model specification and included a separate regressor representing all stimuli of all conditions (ALL) and additional regressors for the individual conditions ActA, ActN, AbstA, AbstN. To avoid the issue of collinearity between regressors within dcm-GLM, which would interfere with the definition and extraction of volumes of interest, we also specified a second GLM matrix (voi-GLM), that only included a separate regressor representing all stimuli of all conditions (ALL) and an additional regressor for the main effect of concreteness (by modeling conditions ActA and ActN). The voi-GLM matrix was only used to extract volumes of interest and was not directly entered during DCM model specification.

In both the voi-GLM and the dcm-GLM, the time series of each participant were high-pass filtered at 67 s and pre-whitened by means of an autoregressive model AR(1). Evoked responses were modeled with the canonical haemodynamic response function, time-locked to the onset of auditory sentence presentation. We modeled the 9 functional scanning sessions as one single concatenated session and we included 9 additional constant regressors, each with values of 1 for the scans of one session and 0 for the other scans, to account for the separate functional scanning sessions. Global effects were removed using a voxel-level linear model of the global signal (Macey et al., 2004) to reduce spike amplitude corresponding to the transitions between sessions in the concatenated time series.

Subject-specific volumes of interest representing the brain regions included in the dynamic causal models were defined through small volume correction, based on first-level *t*-Student contrasts within voi-GLM. Volumes of interest for the four brain regions constituting the left-hemispheric fronto-parieto-temporal system, namely the *pars triangularis* of the inferior frontal gyrus (LIFG), the dorsal precentral gyrus (LdPCG), the supramarginal gyrus (LSMG), and the posterior inferior temporal gyrus (LpITG), were extracted from the main effect of concreteness (action-related > abstract: (ActA + ActN) − (AbstA + AbstN)). The coordinates of these four brain regions were chosen on the basis of the activations action-related > abstract in the second-level General Linear Model ANOVA (see Table 2). In addition, a volume of interest corresponding to the left anterior superior temporal gyrus (LSTG), was extracted from the main effect of all conditions (ActA + ActN + AbstA + AbstN). The LSTG was the region of greatest activation in the F-contrast spanning all experimental conditions in the second-level General Linear Model ANOVA ($x = -54$, $y = -16$, $z = 0$; $F(72,1207) = 27.15$), and was chosen as the direct input of the auditory stimulation, irrespective of the different experimental conditions.

The *t*-Student contrasts were first thresholded at $p = 1$. We then defined spherical volumes (radius = 12 mm) around the group-level stereotactic coordinates of the five brain regions, and extracted the maximum activation peak for each subject. We also checked that the subject-specific coordinates identified through this procedure actually corresponded to the same anatomical location represented by the group-level coordinates. We extracted spherical volumes of interest of 6-mm radius centred on the identified subject-specific coordinates. The volumes of interest were corrected for the effects of interest.

Also for the DCM analysis we adopted a two-stage random-effects approach. At the single-subject level, we defined a dynamic causal model for each participant, based on dcm-GLM, in which ALL provided direct input to the LSTG and the experimental conditions ActA, ActN, AbstA, AbstN were allowed to separately modulate all the connections in the system. Two different connection configurations were estimated for the dynamic causal model: 1) A fully connected and modulated configuration; 2) A more specific configuration based on known neuroanatomical and functional connectivity (Petrides and Pandya, 2008; Rizzolatti and Craighero, 2004), including the following connections (→: unidirectional; ↔: bidirectional): LSTG → LIFG; LSTG → LpITG; LIFG ↔ LdPCG; LIFG ↔ LSMG; LIFG ↔ LpITG; LdPCG ↔ LSMG; LSMG ↔ LpITG. We then used Bayesian model comparison (Penny et al., 2004) to select the most accurate and/or parsimonious of the two connection configurations for each of the two dynamic causal models. On this basis, we selected Configuration 2 (see Results section). At the second level, the DCM average function was then used to obtain group-level parameters for each dynamic causal model, i.e. average Bayesian weighted connection strengths and Bayesian posterior probabilities. We report Bayesian weighted connection strengths (Hz) and posterior probabilities ($P > 0.95$) for the direct effects on the input region and for the intrinsic connections. For each connection, we also computed two-tailed contrasts between experimental conditions for the condition-specific modulatory effects, and obtained the corresponding posterior densities: 1) action-related vs. abstract: (ActA + ActN) − (AbstA + AbstN); 2) specific concreteness by polarity interaction effect for action-related affirmative sentences: (ActA − ActN) − (AbstA − AbstN).

In addition, we also performed classical statistical analyses outside SPM on the arithmetic (non-Bayesian) means of the subject-specific intrinsic and modulatory connection strengths ($n = 18$). For both connection strength types, we first used a Shapiro–Wilk normality test to check the normality of the distribution of the values pertaining to the strength of each individual connection for all subjects. Given a prevalently non-normal distribution of the connection strength values, we then adopted a non-parametric statistical approach. For the intrinsic connection strengths, we applied Wilcoxon signed-rank one-sample tests of means, and we tested the alternative hypothesis that each connection strength was significantly greater than zero. For the modulatory connection strengths, we calculated for each individual connection a 2 by 2 factorial ANOVA on rank-transformed data; for each individual connection strength, we tested the main effect of concreteness and the concreteness by polarity interaction. To account for multiple comparisons (contrasts on 12 connections in Configuration2), we calculated FDR (Benjamini and Hochberg, 1995) corrected alpha values (Tables 4, 5).

Results

Behavioral data collected after fMRI data acquisition

Once the fMRI data acquisition was completed, all participants declared being unaware of the grouping of sentences into the action-

Table 1
Main effects of polarity

Brain region	*Z* score	*x, y, z*
Deactivations: negative > affirmative sentences		
L pallidum	−4.50	−24, −12,0
R MFG	−5.11	36, 16, 32
R MOG	−4.42	38, −80, 40

Effects at $P < 0.05$, corrected for multiple comparisons. L, left; R, right; MFG, middle frontal gyrus; MOG, middle occipital gyrus.

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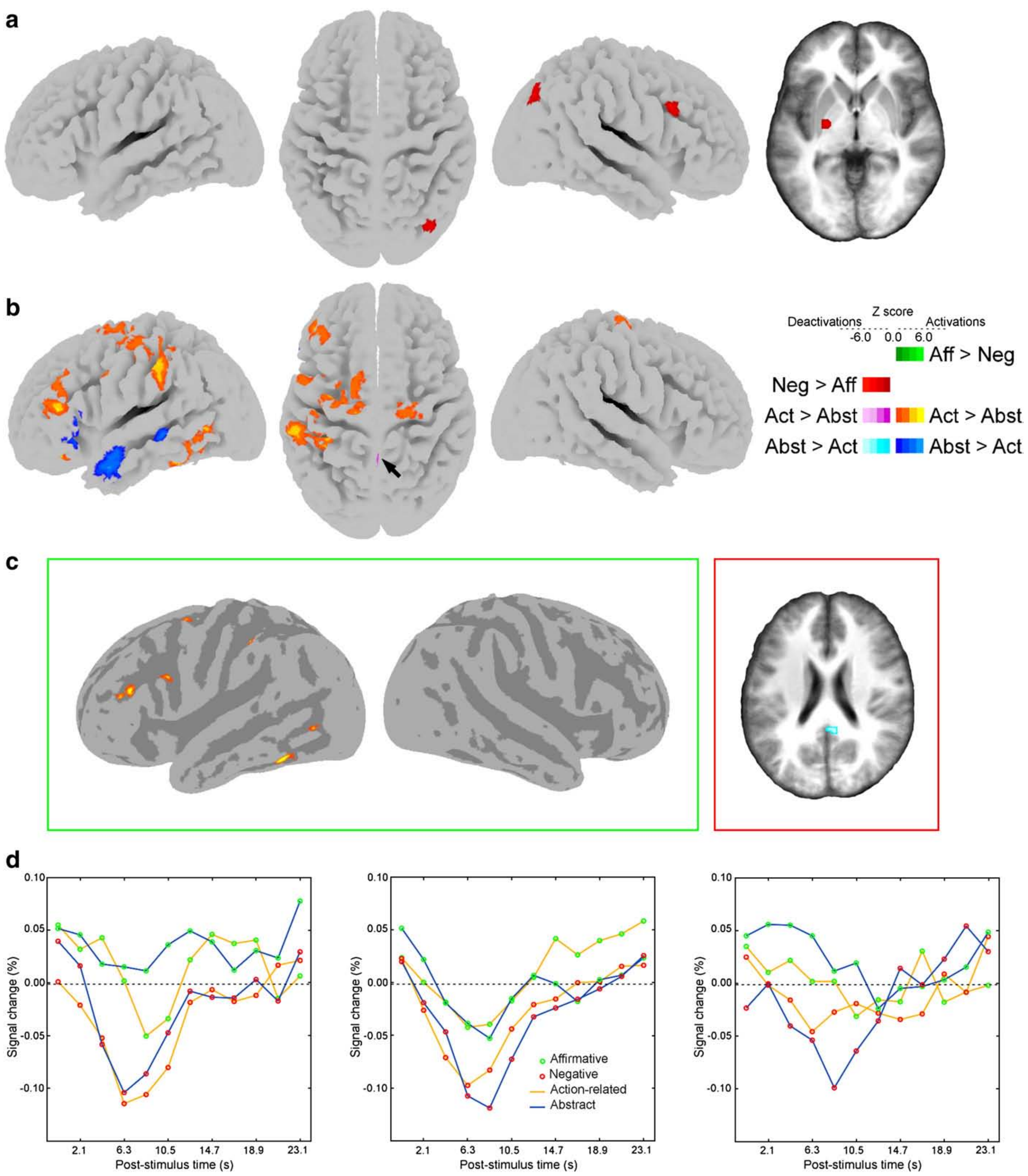

Fig. 1. Reduced activations in sentential negation. Significant effects ($P<0.05$, False Discover Rate (FDR) correction) are displayed on fiducial and inflated cortical renderings, and on axial slices of the participants' average anatomical image. (A) Deactivations elicited by negative sentences (Neg>Aff, red color scale). (B) Activations (Act>Abst, orange color scale) or deactivations (Act>Abst, magenta color scale, black arrow) elicited by action-related sentences, or activations elicited by abstract sentences (Abst>Act, blue color scale). (C) Specific effects of polarity (affirmation vs. negation) on the level of concreteness. Compared to negation, affirmation (as symbolized by the frame in green color) of action-related sentences elicited signal increases in left fronto-parieto-temporal areas. In turn, signal decreases in the posterior cingulate cortex were found for negation vs. affirmation of abstract sentences (cyan color scale, red frame). The lateral cortical views have been slightly rotated to make the activation in the left inferior temporal gyrus visible. (D) Haemodynamic deactivations for negative sentences compared to affirmative sentences, irrespective of the level of concreteness (action-related vs. abstract), in the right middle frontal gyrus (left), in the right middle occipital gyrus (middle) and in the left pallidum (right). Average post-stimulus percent signal changes with respect to whole-brain mean are plotted every 2100 ms post-stimulus time bin, with color combinations reflecting the factorial experimental design: action-related (orange lines); abstract (blue lines); affirmative (green circles); negative (red circles).

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related vs abstract condition. Some of them, however, noticed that the same sentences were presented both in the affirmative and in the negative form. Immediately after fMRI data acquisition, participants were also asked to recall the highest number of sentences or part of sentences they could remember. On average they were able to recall 9.24% (SD=4.90) of all the heard sentences (22.17 sentences out of a total of 240 sentences). The number of recalled sentences by experimental condition was on average, ActA: 8.50 (SD=5.23); ActN: 2.67 (SD=3.99); AbstA: 4.17 (SD=3.13); AbstN: 1.61 (SD=2.03). The number of recalled sentences by experimental condition was entered in a 2×2 ANOVA (Factors: concreteness (action-related or abstract) and polarity (affirmative or negative)). The main effects of concreteness ($P=0.003$, $F(1,17)=11.81$) and polarity ($P=0.0001$, $F(1,17)=26.64$) were both significant. The interaction concreteness by polarity was also significant ($P=0.02$, $F(1,17)=6.30$). It must be underlined that the main effect of polarity and consequently also the interaction may have been biased by the fact that, as noted above, some subjects noticed that the same sentences were presented both in the affirmative and in the negative form. In those cases, a measure of "true" recall for affirmative vs. negative sentences could not be obtained.

Main effects of polarity and concreteness

The first aim of our study was to assess the main effects of polarity independently of the level of concreteness (Table 1). Compared to negative sentences, affirmative sentences were associated with a higher signal in the right middle frontal gyrus, in the right middle occipital gyrus, and in the left pallidum. By inspecting the time-course of the haemodynamic responses in these brain regions, we found that the higher signal for affirmative sentences was in fact due to a greater deactivation for negative sentences relative to the whole-brain mean signal (Figs. 1A, D). In turn, no higher signal was found for negative sentences compared to affirmative sentences.

We also assessed the main effects of concreteness independently of the level of polarity (Fig. 1B). Compared to abstract sentences, action-related sentences activated a predominantly left-lateralized fronto-parieto-temporal network. This network closely corresponds to the system for action representation activated by action-related sentences in Tettamanti et al. (2005), (Table 2A). Compared to action-related sentences, abstract sentences showed increased signal in the left ventral inferior frontal gyrus, the left inferior and middle temporal gyri, and the posterior cingulate cortex (Table 2B). The latter brain region actually showed a higher deactivation for action-related vs. abstract sentences (Table 2C).

Table 2
Main effects of concreteness

Brain region	*Z* score	*x, y, z*
(A) Activations: action-related>abstract sentences		
L IFG (PB)	7.34	−30, 34, −12
L IFG (PT)	5.51	−48, 36, 12§
L vPCG	4.26	−56, 4, 36
L dPCG	4.81	−36, −12, 56§
L aIPS	3.91	−46, −38, 44§
L IPL (SMG)	4.84	−60, −32, 40§
L pMTG	4.42	−54, −64, 0§
L aITG	5.26	−38, −16, −28
L pITG	4.60	−52, −60, −12§
R dPCG	4.04	26, −18, 64
(B) Activations: abstract>action-related sentences		
L IFG (PB)	5.26	−48, 24, −8
L IFG (PT)	3.96	−58, 22, 4
L aMTG	5.16	−50, −4, −28
L pMTG	4.79	−52, −36, −8
L aITG	4.01	−50, 8, −36
(C) Deactivations: action-related>abstract sentences		
R/L pCC	−4.10	0, −52, 32‡

Effects at $P<0.05$, corrected for multiple comparisons. §These activations fall within the action-representation system activated by action-related sentences in our previous study; ‡These activations coincide with those activated by abstract sentences in our previous study (Tettamanti et al., 2005; see also Materials and methods). a- (prefix), anterior; p- (prefix), posterior; v- (prefix), ventral; d- (prefix), dorsal; IFG, inferior frontal gyrus; PB, *pars orbitalis*; PT, *pars triangularis*; PCG, precentral gyrus; IPS, intraparietal sulcus; IPL, inferior parietal lobule; SMG, supramarginal gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; CC, cingulate cortex.

Table 3
Specific effects of polarity on the level of concreteness

Brain region	*Z* score	*x, y, z*
(A) Activations: specific for action-related affirmative sentences		
L IFG (PT)	3.01	−40, 28, 16§
L IFG (PO)	2.98	−48, 8, 24§
L dPCG	3.25	−28, −2, 56§
L IPL	3.13	−56, −34, 52§
L pMTG	2.91	−52, −66, 8§
L pITG	3.02	−48, −50, −16§
(B) Deactivations: specific for abstract negative sentences		
R/L pCC	−3.62	6, −44, 24‡

Effects at $P<0.05$, corrected for multiple comparisons. §These activations fall within the action-representation system activated by action-related sentences in our previous study; ‡These activations coincide with those activated by abstract sentences in our previous study (Tettamanti et al., 2005; see also Materials and methods). PO, *pars opercularis*.

Interaction effects between polarity and concreteness

The second aim of our study was to assess whether the action-representation system underlying action-related sentence processing and the neural system underlying abstract sentence processing were specifically modulated by sentential negation. The interactions between polarity and concreteness revealed significant effects within both systems (Table 3; Fig. 1C). The comparison testing for the specific interaction of polarity with abstract sentences revealed an effect in the posterior cingulate cortex, which consisted in a stronger deactivation for abstract negative sentences. The interaction between polarity and action-related sentences, instead, revealed significant effects in left fronto-parieto-temporal regions, consisting in a signal reduction for negative vs. affirmative sentences.

Analysis of effective connectivity

The third aim of our study was to measure functional integration within the left-hemispheric system for action representation. To this aim, we used DCM to define a connectivity model linking the left inferior frontal gyrus, dorsal precentral gyrus, supramarginal gyrus, and posterior inferior temporal gyrus. The model also included the left superior temporal gyrus as the brain area of stimulus-independent psychological (auditory) input. DCM was used to test whether the connection strengths between fronto-parieto-temporal areas were stronger for action-related vs. abstract sentences, and whether, due to a concreteness by polarity interaction, the connection strengths were specifically stronger for action-related affirmative sentences.

Two distinct connection configurations were compared for the dynamic causal model at the first-level. Brain regions were fully connected and modulated in Configuration 1. Configuration 2 was instead based on known (Petrides and Pandya, 2008; Rizzolatti and Craighero, 2004) neuroanatomical and functional connectivity patterns (Fig. 2a). We then selected the configurations displaying the strongest evidence using Bayesian model comparison. In all 18 subjects, the Bayes factors indicated very strong evidence in favour of Configuration 2. On this basis, Configuration 2 was selected.

At the second level, for Configuration 2, the intrinsic, condition-independent connectivity was found to be significant for all the connections included in the dynamic causal model (Fig. 2a). However,

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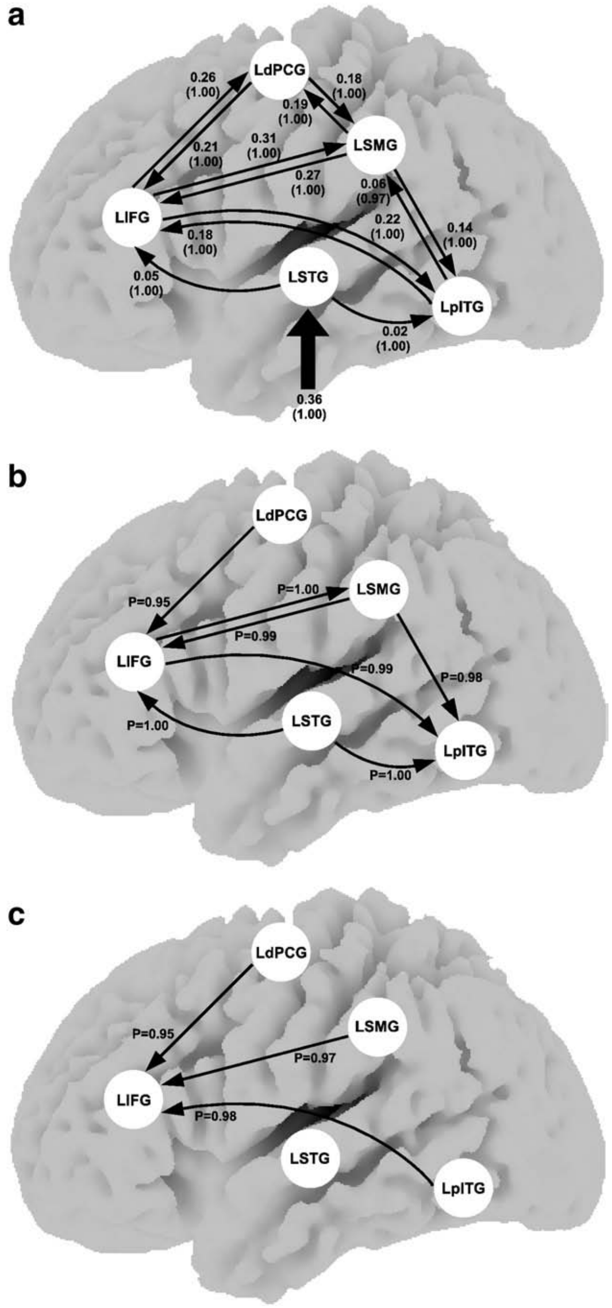

Fig. 2. Modulations of connection strengths in sentential negation. Effective connectivity in the left-hemispheric system for action representation, including the inferior frontal gyrus (LIFG), the dorsal precentral gyrus (LdPCG), the supramarginal gyrus (LSMG), and the posterior inferior temporal gyrus (LpITG). (a) Psychological driving input (thick arrow) in the left superior temporal gyrus (LSTG) and intrinsic, condition-independent connections between areas of the brain system (thin arrows) are rendered onto the cortical surface. Average, Bayesian weighted intrinsic connection strengths (Hz) and associated posterior probabilities (in brackets) are indicated close to the corresponding connection arrows. (b) Stronger modulations of connection strengths for action-related vs abstract sentences. (c) Stronger modulations of connection strengths for action-related vs. abstract sentences in the case of affirmative than in the case of negative sentences. For b and c, posterior densities for the contrasts between experimental conditions are indicated close to the corresponding connection arrows. Throughout the figure, only the connections parameters displaying $P>0.95$ are shown.

only a subset of these connections were also significant in the classical (non-Bayesian) second-level analysis (Table 4).

Table 4
Intrinsic, condition-independent connection strengths

Connection	Mean strength (Hz)	St. Dev.	Wilcoxon
LIFG → LdPCG	0.1486	0.2067	***P*=0.0030**
LIFG → LSMG	0.1237	0.1541	***P*=0.0039**
LIFG → LpITG	0.0966	0.1064	***P*=0.0003**
LdPCG → LIFG	0.0107	0.0765	*P*=0.2710
LdPCG → LSMG	0.0519	0.0615	***P*=0.0002**
LSMG → LIFG	0.0335	0.0884	*P*=0.1113
LSMG → LdPCG	0.0620	0.0740	***P*=0.0009**
LSMG → LpITG	0.0520	0.0783	***P*=0.0030**
LpITG → LIFG	0.0232	0.0607	*P*=0.1113
LpITG → LSMG	0.0826	0.1543	***P*=0.0132**
LSTG → LIFG	0.0500	0.0815	***P*=0.0118**
LSTG → LpITG	0.0189	0.0602	*P*=0.0637

Arithmetic (non-Bayesian) values and statistics for connections displaying changes with posterior probability $P>0.95$ (see Fig. 2a). St. Dev., Standard Deviation; LIFG, left inferior frontal gyrus; LdPCG, left dorsal precentral gyrus; LSMG, left supramarginal gyrus; LpITG, left posterior inferior temporal gyrus; LSTG, left superior temporal gyrus. Significant effects ($P<0.05$, corrected for multiple comparisons) are shown in bold.

With respect to condition-dependent modulations, we found that the main effect of concreteness significantly modulated the connection strengths of a subset (7 out of 12) of connections in the dynamic causal model (Fig. 2b), indicating that the activity of the brain regions constituting the action-representation system is functionally more integrated when processing action-related than abstract sentences. Modulations were also significant for four of this subset of seven connections in the classical (non-Bayesian) second-level analysis (Table 5A). Most importantly, we found that, within the action-representation system, the modulatory effects for action-related vs. abstract sentences were stronger in the case of affirmative than negative sentences. The analysis of the interaction effects between concreteness and polarity revealed significant effects in three connections involving the left inferior frontal, the dorsal precentral, the supramarginal, and the posterior inferior temporal gyri (Fig. 2c). However, only the connection from the left supramarginal gyrus to the left inferior frontal gyrus, and the connection from the left posterior inferior temporal gyrus to the left inferior frontal gyrus, presented a significant modulation interaction also in the classical (non-Bayesian) second-level analysis (Table 5B).

Summary

In summary, irrespective of the level of concreteness (action-related vs. abstract), sentential negation was associated with a deactivation of pallido-cortical areas. Crucially, negation induced distinct effects for action-related vs. abstract sentences. In the case of negative action-related sentences, a reduction of both activations and connection strengths occurred within a left-hemispheric fronto-parieto-temporal system. For negative abstract sentences, there was a deactivation of the posterior cingulate cortex.

Table 5
Contrasts of connection strength modulations between conditions

Connection	ANOVA on rank-transformed data
(A) Main effect: action-related>abstract sentences	
LIFG → LSMG	$\mathbf{P=9.0\times10^{-6}}$
LIFG → LpITG	***P*=0.0024**
LdPCG → LIFG	*P*=0.0425
LSMG → LIFG	*P*=0.0872
LSMG → LpITG	*P*=0.0589
LSTG → LIFG	$\mathbf{P=1.4\times10^{-5}}$
LSTG → LpITG	***P*=0.0010**
(B) Interaction specific for action-related affirmative sentences	
LdPCG → LIFG	*P*=0.5131
LSMG → LIFG	***P*=0.0114**
LSTG → LIFG	***P*=0.0097**

Arithmetic (non-Bayesian) statistics for connections also showing a significant effect in the Bayesian analysis at $P>0.95$ (see Figs. 2b, c). Significant effects ($P<0.05$, corrected for multiple comparisons) are shown in bold.

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Discussion

The present results represent a preliminary step toward the understanding of the neural mechanisms of sentential negation. Overall, the results do not support the hypothesis of a greater processing load associated to negative sentences, and are in line with the idea of a reduced access to the negated information. A theoretical model on negation has been recently advanced (Kaup et al., 2007), which assumes that the process of understanding a negative sentence (e.g. "John has not left") can be reconducted to a process of deviation detection. In a first step, the counterfactual state of affairs is mentally simulated (e.g. a simulation of "John has left"). In a second step, the mental simulation reflects the factual state of affairs (e.g. "John has not left"). A comparison of the two simulations then allows the comprehender to determine the exact content of the original negative sentence. According to the two-step simulation hypothesis, the neural representations of the negated information should be activated during the first step and less or not at all activated during the second step. Our results do not provide direct evidence in support or against this view, as we only found evidence of reduced activation in semantic representation systems and of pallido-cortical deactivations. However, it is of course possible that the activations corresponding to the first simulation stage are short lived, and that they could not be detected due to the coarse temporal resolution of fMRI. Furthermore, the reduced activations in semantic representation systems may stem either from a reduced response amplitude or from a shorter response duration or from both. Further studies will be required to investigate these possibilities.

At a broad level of analysis, negative sentences were characterized by activation decreases with respect to affirmative sentences. These activation decreases were characterized by two distinct brain activity patterns. The first pattern consisted of an haemodynamic deactivation and was observed for negative sentences irrespective of the level of concreteness in pallido-cortical areas, and, for abstract negative sentences only, in the posterior cingulate cortex. The second pattern consisted of a reduction of the haemodynamic response and was observed specifically for action-related negative sentences in left fronto-parieto-temporal areas. A conservative interpretation for these activation decreases is that the brain responses were reduced because in the case of negative sentences the participants were simply diverted from a linguistic analysis of the sentences, failing to attend to them after negation was delivered. This is in principle compatible with the results of the behavioral analysis, showing higher recall rates for affirmative vs. negative sentences after fMRI data acquisition. However, this interpretation seems unlikely, given the lack of significant activations in left perisylvian language areas in the main effect of affirmation minus negation, activations that were to be expected in the presence of a diminished linguistic processing for negative sentences. A further alternative explanation for the signal reductions, particularly in left fronto-parieto-temporal areas would be that, assuming that the comprehension of an action described by linguistic utterances is not an inherent process to language comprehension but rather consists of accessory and voluntary mental imagery, these accessory processes are inhibited in the case of negation. This possibility cannot be excluded but seems implausible, in the light of the evidence that neurophysiological correlates of action simulation are rapidly and automatically activated after action-word presentation and that these simulation processes modulate body-part specific motor responses in dual-task conditions (Pulvermuller, 2005).

As for the first signal reduction pattern, i.e. the deactivations found for negative vs. affirmative sentences, the results are open to different interpretations. "True" haemodynamic deactivations have been substantially attributed to a concomitant decrease in neuronal activity below spontaneous baseline activity that triggers a local reduction in cerebral blood flow (Shmuel et al., 2006). This may speak for a decrease of neuronal activity in the left pallidum, and in the right middle frontal and middle occipital gyri during the processing of negative sentences, irrespective of the level of concreteness. Due to the paucity of consolidated evidence in the literature about the anatomo-functional correlates of negation, we had no a priori expectations on the localization of the main effects of polarity. However, it is quite intriguing that the basal ganglia have been specifically implicated in executive semantic functions, either as a mechanism regulating the release or selection of cortically generated lexical items for production after semantic monitoring (Crosson, 1985; Wallesch and Papagno, 1988), or as responsible for the attentional regulation of the semantic network (Copland, 2003). The deactivation of the left pallidum may therefore reflect a reduced semantic processing in the context of negative sentences, compatible with the reduced accessibility hypothesis.

A deactivation pattern was also observed in the posterior cingulate cortex. As a main effect, this brain region was more deactivated by action-related than by abstract sentences. However, the posterior cingulate cortex also presented a significant polarity by concreteness interaction, an effect that was dominated by a stronger deactivation for abstract negative than for abstract affirmative sentences. In spite of its apparent complexity, this deactivation pattern is not surprising. We had specifically hypothesized that abstract negative sentences would modulate the posterior cingulate cortex based on the observation of an abstract-related effect in this brain region in previous studies (Tettamanti et al., 2005; Tyler et al., 2001). The posterior cingulate cortex is a key component of the default mode brain system, a tonically active system that continuously gathers information about the world around and within us, and that becomes deactivated during goal-directed actions (Greicius and Menon, 2004; Gusnard and Raichle, 2001; McKiernan et al., 2003; Raichle et al., 2001). A relative absence of goal-directed action plans may be associated to abstract vs. action-related sentences. This explains why as a main effect, abstract sentences deactivated the posterior cingulate cortex less than action-related sentences. When abstract sentences are negative, however, the negation may act as a signal that such an absence of goal-directed action plans may be violated: the alteration of this balance would then elicit a greater deactivation of the posterior cingulate cortex.

As for the second signal reduction pattern, i.e. the reduction of the haemodynamic response specific to action-related negative sentences in left fronto-parieto-temporal areas, the results are in close agreement with our initial hypothesis. There is a strong convergence between the neuroanatomical location of these effects and the location of the effects found for action-related sentences in our previous study (Tettamanti et al., 2005). The present findings therefore suggest that the negation of action-related sentences induces a relatively weaker activation of the action-representation system involved in embodied language representations (Gallese, 2007; Rizzolatti and Craighero, 2004). The signal reduction in the left fronto-parieto-temporal system is consistent with the view that the access to action representations that are usually engaged in processing a sentence like "I push the button" is significantly reduced when processing the corresponding negative sentence, i.e. "I do not push the button".

Embodied language theories imply that language comprehension is mediated by the fast and automatic cross-talk between speech parsing networks, extracting phonological, morphological, syntactic and semantic information, and perceptuo-motor representations (Barsalou, 1999; Glenberg and Kaschak, 2002). These perceptuo-motor representations reflect the specific semantic content conveyed, such as motor circuits for action-related language (Pulvermuller, 2005), distinct components of the posterior temporal cortex for colour vs. form words (Pulvermuller and Hauk, 2006), and olfactory cortex for odour-related words (Gonzalez et al., 2006). If this view is correct, measures of functional integration that can be applied to fMRI data, such as DCM (Friston et al., 2003; Lee et al., 2006), should reveal modulations of the cross-talk between speech parsing and semantic

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brain regions that are dependent on the specific semantic content expressed by linguistic utterances. For instance, the comprehension of action-related vs. abstract sentences should be associated with a relatively stronger functional integration, i.e. positive coupling, between perisylvian regions and the action-representation system. Using DCM, we specifically tested whether the degree of functional integration between the left inferior frontal gyrus and the left fronto-parieto-temporal system, including the dorsal premotor cortex, the supramarginal gyrus, and the left posterior inferior temporal gyrus, was more positive for processing action-related vs. abstract sentences. Our results demonstrated that this is indeed the case and complement the findings of more classical analyses of functional specialization underlying action-related conceptual representations (Pulvermueller, 2005). These results are also in agreement with previous reports of a more positive functional integration among left fronto-parieto-temporal for action-related semantic processing, in particular for tools vs. animals (Noppeney et al., 2006; Vitali et al., 2005).

Most importantly then, the results of our analysis of functional integration showed that the modulatory effects for action-related vs. abstract sentences in a subset of connections within the left fronto-parieto-temporal system were stronger in the case of affirmative than in the case of negative sentences. This provides compelling evidence in favour of the view that the spread of activation into conceptual representation systems is reduced in the case of sentential negation. Such a reduced functional integration appears to constitute a plausible neurophysiological correlate for the reduced access to negated information as postulated on the basis of psycholinguistic evidence.

These modulations of the action-representation system go back to the most intriguing question about sentential negation: what do we understand when we understand negation? The data of the present study suggest a neurophysiological model in which negation is encoded by our brain in terms of a reduced activation of the areas representing the negated information. This principle is clearly illustrated by action-related sentences. While in the affirmative form, listening to action-related sentences triggers the representation of an action's outcome through the recruitment of the cortical action-representation system, in the negative form, the mental simulation of the action's outcome may be at least partially suppressed, giving rise to the subjective experience of negation. In this view, negation appears to offer a new perspective on the link between human language as a formal system and our representation of the world.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.08.004.

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