

Demand on Verbal Working Memory Delays Haemodynamic Response in the Inferior Prefrontal Cortex

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Abstract: Event-related functional magnetic resonance imaging was used to test the involvement of the inferior prefrontal cortex in verbal working memory. Pairs of French nouns were presented to ten native French speakers who had to make semantic or grammatical gender decisions. Verbal working memory involvement was manipulated by making the categorization of the second noun optional. Decisions could be made after processing the first noun only (RELEASE condition) or after processing the two nouns (HOLD condition). Reaction times suggested faster processing for gender than for semantic category in RELEASE. Despite the absence of anatomical difference across tasks and conditions in the wide activated network, the haemodynamic response peak latencies of the inferior prefrontal cortex were significantly delayed in HOLD versus RELEASE while no such peak delay was observed in the superior temporal gyrus. Interestingly, this pattern did not interact with language tasks. This study shows that cognitive manipulation can influence haemodynamic time-course and suggests that the main cognitive process determining inferior prefrontal activation is verbal working memory rather than specific linguistic processes such as grammatical or semantic analysis. *Hum. Brain Mapping* 19:37–46, 2003.

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Key words: verbal working memory; inferior prefrontal cortex; gender processing; semantic processing; event-related fMRI; evoked haemodynamic response

INTRODUCTION

The left inferior prefrontal cortex (IPC) has been hypothesized to take part in numerous aspects of language

processing. After it was baptized the “centre for motor images of words” by Paul Broca [1861], clinical neuropsychologists soon extended the involvement of the left IPC to syntactic processing because lesions in this location often caused agrammatism [e.g., Taubner et al., 1999]. Overall, neuropsychological data from patient studies did not provide a clear structure-function interpretational framework for the organization of language in the brain, however, and some fundamental debates continue to rage [e.g., Grodzinsky, 2000].

Neuroimaging studies have even further diversified the hypothetical roles of the IPC by showing its acti-

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vation when different aspects of linguistic representations are accessed. First, experiments involving phoneme detection [Binder, 1997; Démonet et al., 1992, 1994; Thierry et al., 1999], non-word repetition [Thierry et al., 1999], and more generally phonological rehearsal tasks favoring the involvement of the phonological loop [Paulesu et al., 1993] have demonstrated selective activations in the dorsal aspects of the left IPC. Second, studies exploring neural correlates of sentence comprehension have suggested a selective involvement of the left IPC [Caplan et al., 2000; Dapretto and Bookheimer, 1999], including Broca's area (Brodmann's Area, BA 44/45) and the inner part of the frontal operculum and the anterior insula [Moro et al., 2001] in syntactic processing [Caplan et al., 1998, 2000; Caplan and Waters, 1999; Just et al., 1996]. Third, the IPC has been proposed to take part in the encoding [Demb et al., 1995] and retrieval [Dapretto and Bookheimer, 1999; Gabrieli et al., 1998] of semantic knowledge, although this has been extensively debated [see Démonet and Thierry, 2001; Thompson-Schill et al., 1997].

In other words, the left IPC might be involved at all the different stages of language processing that have been postulated by cognitive models, i.e., phonology, syntax, and semantics [Levelt et al., 1999; Marslen-Wilson, 1989; McClelland and Elman, 1986; Norris, 1994]. Therefore, if one region in the brain contradicts the hypotheses of Localisationism, it certainly is Broca's area.

However, an interesting hypothesis is that the involvement of the IPC is not selective to phonology, syntax, and semantics but rather relates to its central role in verbal working memory (VWM), which is the subsystem for working memory devoted to verbal information [Baddeley, 1998]. Indeed, tasks such as phonological rehearsal, syntactic structure screening, semantic selection, inner speech, etc., all involve VWM to various extents and this might explain why the IPC is very often found activated [Caplan et al., 2000; Caplan and Waters, 1999; Gabrieli et al., 1998; Paulesu et al., 1993]. Moreover, several experiments have shown selective activation of the IPC in relation to the manipulation of VWM load [e.g., Braver et al., 1997; Fiez et al., 1996].

Here, we used event-related functional magnetic resonance imaging (ER-fMRI) to further investigate the involvement of the IPC in VWM. On the one hand, we varied VWM demands by manipulating the number of verbal items (one or two) that needed to be categorized in order to complete the task. Participants were presented with noun-pairs. They could either make a decision without processing the second noun

(RELEASE condition) or needed to hold the second noun in VWM in order to respond (HOLD condition). On the other hand, we used two different language tasks, a gender one and a semantic one, to test whether VWM demands would interact with the linguistic process in focus. This made our design 2×2 factorial.

Given the extended involvement of VWM in the HOLD condition, we hypothesized that reaction times would be longer in HOLD than RELEASE, and that the IPC would be activated for a longer period of time as compared to other structures involved in perceptual processes (such as the superior temporal gyrus, STG). The latter effect should result in delayed haemodynamic peak latencies.

Language task differences could relate to the fact that the grammatical gender of nouns is an overlearned and mandatory feature of French whereas natural vs. artifact categorization requires access to a wider and multi-dimensional domain of knowledge. Two previous studies have reported a trend for faster reaction time in gender decision tasks as compared to semantic categorization [Miceli et al., 2002; Schmitt et al., 2001]. We, therefore, hypothesized that grammatical gender would be retrieved before lexical semantic information. Given the inconsistency of results concerning the involvement of the IPC in syntactic and semantic processing and given the fact that we used noun-pairs as opposed to sentences, we did not make any hypotheses concerning the effects of language tasks on activation patterns.

SUBJECTS AND METHODS

Subjects

The participants were 24 French volunteers (12 men, 12 women, mean age 25 ± 3 years) in the behavioral study and 10 (5 men, 5 women, mean age 26.1 ± 1.8 years) in the fMRI experiment. They gave informed consent to participate in the experiment, which had been approved by a local ethics committee.

Stimuli

In the behavioral study, the stimuli were 280 monosyllabic singular French nouns associated in pairs; a subgroup of 120 was used in the ER-fMRI experiment. All nouns were selected from the Brulex database [Content et al., 1990]. Half of the words corresponded to artifacts and the other half referred to natural objects. Each semantic group featured an equal number of feminine and masculine nouns. In order to avoid any interference between natural (semantic) gender

and syntactic gender, animal names displaying natural gender were excluded (gender marking can then be considered as syntactic information free of semantic judgment [Hagoort and Brown, 1999]).

Lexical frequency was between 150 and 500. Eighty-three percent of the words had only one standard meaning, 11% had one semantic variant, and 5% had two [Content et al., 1990; Robert, 1986]. Eighty-seven percent of the nouns had a unique grammatical gender, 13% had a “dominant” gender (the homophonic noun with opposite gender was far less frequent).

Words were produced by a female speaker, digitized at 22 kHz, normalized, amplified, and digitally resampled to 500 msec. Sound files were stretched or expanded by no more than 5%. They were then pseudo-randomly assembled in pairs lasting for 1,040 msec, the two nouns in a pair being separated by 40 msec. Semantic and phonological links were avoided within a pair and all category combinations were in equal proportions (i.e., 25% feminine–feminine, 25% feminine–masculine, 25% masculine–masculine, and 25% masculine–feminine; and similarly for semantic categories).

Tasks

In each block, participants were asked to monitor the pairs in which both nouns pertained to a specific category (feminine, masculine, natural objects, or artifacts) by pressing keys in the behavioral task and lifting their fingers in the fMRI, e.g., left for “yes” and right for “no.” They were explicitly instructed to respond as soon as they could (e.g., “no” immediately after identifying the first noun as incongruent with the target category).

In each trial, two different situations could arise: (1) the first noun was incongruent with the target category, in which case the participants could respond “no” immediately and there was no need to hold the second noun in VWM (RELEASE condition); or (2) the first noun was congruent, in which case they needed to hold the second noun in VWM until they could reach a decision about its congruency (HOLD condition). The categorization of the second noun in the latter case was enough to make a decision.

In a previous event-related potential experiment using the same design, we showed that participants do abort the processing after categorizing the first noun in the RELEASE condition, as demonstrated by the absence of an N400 component for the second noun in this condition [Thierry et al., 1998].

Procedure

In the behavioral version, subjects were installed in a quiet room and presented with 8 blocks of 70 pairs of nouns. Stimulus Onset Asynchrony (SOA) was set at 2,500 msec. Before each block the experimenter gave the instruction verbally, indicating the target category and corresponding response sides.

In the fMRI version, participants were installed in the scanner and were given the instruction prior to each block through headphones. Six runs of 20 pairs of nouns were delivered at a rate of 1 every 12 sec [Bandettini and Cox, 2000].

In both experiments, type of task (gender or semantic) and response sides were fully counter-balanced across blocks and participants and the same pairs of words were equally used in all conditions. The rate of stimulus presentation and the overall number of stimuli were the only differences between the behavioral and the fMRI experiment.

EHR Recording and Analysis

Haemodynamic Responses were acquired using a 1.5 T Magnetom Vision Siemens Scanner in EPI mode using a single-shot T2*-weighted sequence. Acquisitions provided 6 contiguous transverse slices (FOV 220 mm, thickness 7 mm, TE = 66 msec, TR = 2,000 msec, matrix acquisition 96*128 interpolated to 128*128) in approximately 780 msec and were repeated 6 times after each stimulation. Stimulus delivery occurred every 12 sec in the 1,220-msec silence gap between two acquisitions. Acquisition voxel size was $2.3 \times 1.7 \times 7.0$ mm. The bottom of the lower slice was set 7 mm under AC–PC. Raw images were realigned, normalized and smoothed (FWHM of 6 mm) using SPM99 [Wellcome Institute of Neurology; online at www.fil.ion.ucl.ac.uk; Friston et al., 1995, 1996]. Slice timing correction was deliberately not implemented before image realignment because subjects’ movements were prominent in the $[x, y]$ plane and signals from adjacent cortical regions of interest would have been confounded more than signals from adjacent slices.

Haemodynamic signals were temporally high-pass filtered at $1.5 \cdot 10^{-2}$ Hz and modeled using a half sinusoidal waveform best fitting stimulus rate (half period = 6 sec). Activations were detected in the framework of the general linear model using SPM96 at a threshold of $P < 0.001$ (extension correction of $P < 0.05$; Table I; see Fig. 2) and replicated at a threshold of $P < 0.001$ corrected for multiple comparisons in SPM99.

TABLE I. SPM Results*

	BA	Cluster			Release					Hold							
		P	n	Z	Voxel		Coordinates			Cluster			Voxel		Coordinates		
					P	Z	x	y	z	P	n	Z	P	Z	x	y	z
Gender																	
Left Hemisphere																	
Superior temporal gyrus/ transverse temporal gyrus	BA 29/41	***	371	8.44	***	-8.44	-42	-32	14	***	346	8.80	***	-8.80	-40	-32	14
Superior temporal gyrus/ inferior parietal lobule	BA 13/40				***	-7.81	-48	-44	21				***	-7.60	-50	-44	21
Superior temporal gyrus	BA 22				***	-7.85	-50	-12	7				***	-7.29	-50	-12	7
Thalamus		***	106	7.80	***	-7.80	-10	-22	7	***	137	8.08	***	-8.08	-8	-22	7
Thalamus					***	-6.71	-12	-32	0				***	-7.20	-12	-30	0
Thalamus					***	-5.43	-12	-8	14				***	-6.20	-12	-8	14
Cuneus/lingual gyrus	BA 18	***	326	6.50	***	-6.50	0	-78	7	*	19	4.38	0.063	-4.38	-10	-82	21
Insula/prefrontal cortex	BA 13/44				***	-6.95	-33	22	7				***	-6.95	-39	14	7
Right hemisphere																	
Transverse temporal gyrus	BA 41	***	424	8.38	***	-8.38	38	-36	14	***	444	8.44	***	-8.44	38	-36	14
Superior temporal gyrus/ transverse temporal gyrus	BA 29/41				***	-7.62	48	-26	14				***	-8.13	48	-28	14
Superior temporal gyrus/ insula	BA 22/13				***	-7.64	48	8	0								
Superior temporal gyrus/ insula	BA 13/40												***	-8.04	48	-40	21
Thalamus		***	92	7.15	***	-7.15	8	-20	7	***	463	7.86	***	-7.86	8	-20	7
Thalamus					***	-6.60	12	-30	0				***	-6.68	10	-30	0
Cuneus/lingual gyrus	BA 17/18	***	326	6.50	***	-6.48	8	-68	7				***	-6.68	4	-80	0
Insula/prefrontal cortex	BA 13/44				*	-4.50	41	15	7				*	-4.50	40	15	7
Semantics																	
Left hemisphere																	
Transverse temporal gyrus	BA 41									***	189	8.61	***	-7.69	-48	-22	14
Superior temporal gyrus/ transverse temporal gyrus	BA 29/41				***	-8.94	-42	-32	14				***	-8.61	-40	-34	14
Superior temporal gyrus/ inferior parietal lobule	BA 13/40					-8.09	-48	-42	21				***	-7.16	-48	-44	21
Superior temporal gyrus	BA 22	***	17	7.33	***	-7.33	-48	-12	7	***	24	7.08	***	-7.08	-50	-12	7
Superior temporal gyrus	BA 22					-6.52	-50	0	0				***	-6.52	-50	0	0
Insula	BA 13	**	26	4.88	**	-4.88	-40	12	7	*	23	4.85	**	-4.85	-38	14	7
Insula	BA 13					-4.57	-30	18	7				*	-4.57	-30	18	7
Thalamus		***	111	7.88	***	-7.88	-10	-22	7	***	106	8.26	***	-8.26	-10	-22	7
Thalamus					***	-6.05	-12	-10	14				***	-6.72	-8	-30	0
Thalamus					***	-5.45	-10	-32	0				***	-5.90	-12	-8	14
Lingual gyrus	BA 19	***	17	7.33	***	-5.64	-16	-72	0				***	-7.19	-6	-62	0
Cuneus/lingual gyrus	BA 18	***	26	6.32	***	-6.32	-6	-82	21								
Insula/prefrontal cortex	BA 13/44				***	-6.95	-42	11	7				***	-6.95	-39	16	7
Right hemisphere																	
Transverse temporal gyrus	BA 41									***	237	8.94	***	-7.86	-48	-22	14
Superior temporal gyrus/ transverse temporal gyrus	BA 29/41	***	347	8.70	***	-8.70	40	-36	14	***	374	8.65	***	-8.65	42	-36	14
Superior temporal gyrus/ insula	BA 22/13				***	-7.91	50	-12	7				***	-7.67	48	8	0
Superior temporal gyrus/ insula	BA 13/40												***	-7.65	46	-20	7
Insula	BA 13				***	-8.18	44	-38	21								
Thalamus		***	83	7.24	***	-7.24	8	-22	7	***	113	8.03	***	-8.03	10	-20	7
Thalamus					***	-6.07	12	-28	0				*	-4.81	12	-10	14
Lingual gyrus	BA 19	***	211	7.18	***	-7.18	18	-62	0	***	310	7.71	***	-7.71	16	-62	0
Lingual gyrus	BA 18/19				***	-5.94	6	-80	0								
Cuneus/lingual gyrus	BA 17/18												***	-7.58	2	-76	7
Insula/prefrontal cortex	BA 13/44				*	-4.50	39	18	7				*	-4.50	43	10	7

* Listed structures are highest probability hits in a radius of 5 mm around the activated voxel according to the Talairach and Tournoux Atlas [1988].

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. (Cluster-level statistics are not displayed for prefrontal activation because SPM assimilated corresponding voxels as part of the STG cluster.)

Cluster = cluster-level statistics; n = voxel count; voxel = voxel-level statistics (coordinates are in mm in Talairach space).

Individual haemodynamic responses were averaged in each subject and condition to obtain Evoked Haemodynamic Responses (EHRs [Thierry et al., 1999;

Toni et al., 1999]). EHRs were calculated by averaging adjusted signals recollected from the XA matrix generated by SPM96 using custom Matlab (MathWorks,

Natick, MA) procedures. SPM96 was preferred to SPM99 for this analysis because the adjusted signals can be directly retrieved together with contrast-specific *t* statistics. After slice timing correction, EHRs were spline-interpolated for optimizing temporal resolution down to 150 msec (i.e., not less than slice acquisition duration). EHR peak latencies were then detected for each activated voxel by searching for the maximum of amplitude within the corresponding event-related haemodynamic response and plotted onto high-resolution anatomical slices of one of the subjects (see Fig. 2).

Four volumes of interest, encompassing the 4 regions activated in every subject (i.e., left and right STG and left and right IPC), were defined a priori in Talairach space [Talairach and Tournoux, 1988]. The left STG was delimited by [*x*, *y*, *z*] coordinates in mm as follows: [$-65 < x < -20$], [$-50 < y < -25$], [$-7 < z < 21$]; and encompassed Brodmann's Areas (BAs) 41, 42, 22, and 21. The left inferior prefrontal region was delimited by [*x*, *y*, *z*] coordinates in Talairach space as follows: [$-65 < x < -25$], [$0 < y < 20$], [$-7 < z < 28$]; and encompassed BAs 44, 47, 13. Right homologous volumes were symmetrical in terms of *x* coordinates. EHRs of activated voxels were averaged in each of the four volumes for each individual and their peak latencies determined. A four-factor ANOVA was then performed on regional peak latencies to characterize temporal differences relating to task (two levels), condition (two levels), region (two levels), and hemisphere (two levels, see Fig. 3).

RESULTS

Behavioral results

Hit rates were significantly higher in the semantic task (mean = 93.1% ± 3.7) than the gender task (mean = 91% ± 3.4) [$F(1,23) = 12.75, P = 0.0016$] and significantly higher in HOLD condition (mean = 93.2% ± 3.1) than RELEASE condition (mean = 90.9% ± 2.7) [$F(1,23) = 59.15, P < 0.0001$]. There was a significant task * condition interaction [$F(1,23) = 19.64, P = 0.0002$] showing that Semantic HOLD was the condition in which participants made the fewest errors.

Differences in RTs across tasks (errors being dismissed) were just at significance threshold [$F(1,23) = 4.24, P = 0.051$]. A major effect was found for the HOLD versus RELEASE comparison [$F(1,23) = 412.3, P < 0.0001$; Fig. 1a] as well as a reliable task * condition interaction [$F(1,23) = 30.6, P < 0.0001$; Fig. 1b], indicating that Semantic RELEASE RTs were significantly longer [$F(1,23) = 12.74, P = 0.0013$] than Gender RE-

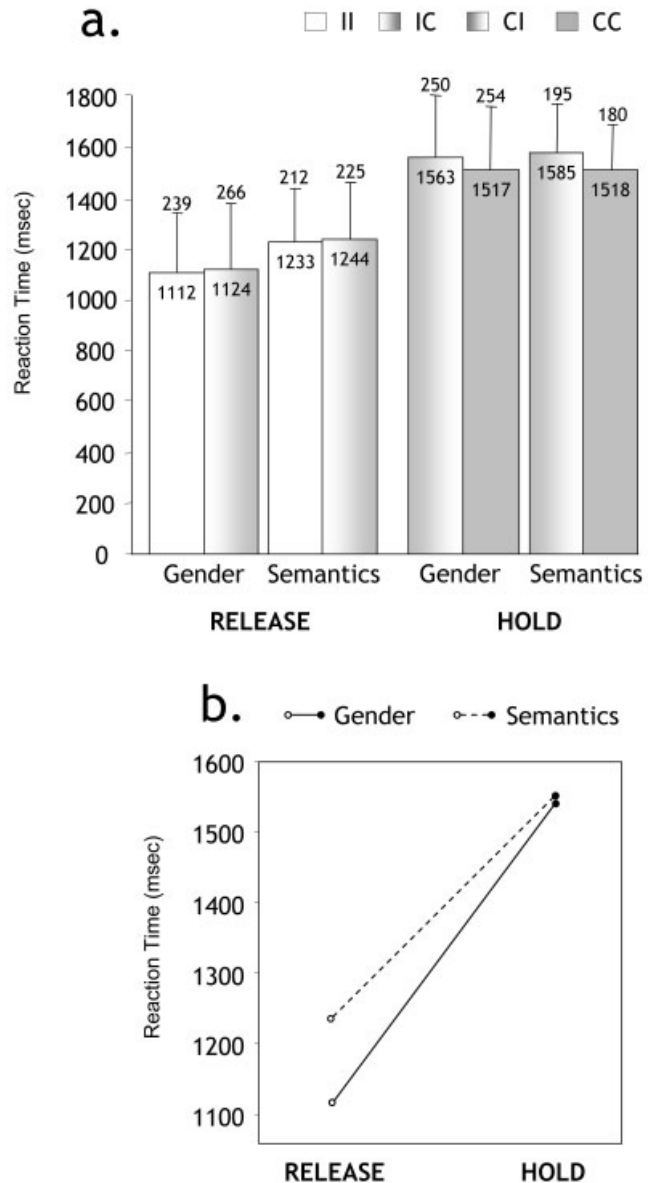


Figure 1.

a: Mean Reaction Times (RTs) in all conditions. Sub-types corresponding to different stimulus combinations in pairs are distinguished (I refers to Incongruent and C to Congruent regarding the target category). Numeric values of mean and standard deviations are displayed within and above each bar, respectively. **b:** Plot of the Task * Condition interaction [$F(1,23) = 30.6, P < 0.0001$].

LEASE RTs in the absence of a significant difference [$F(1,23) = 0.71, P = 0.739$] between Semantic HOLD and Gender HOLD.

Finally, in RELEASE, RTs to Incongruent-Incongruent noun pairs were not significantly different from RTs to Incongruent-Congruent pairs [$F(1,23) = 1.25, P = 0.2746$], but in HOLD, there was a significant dif-

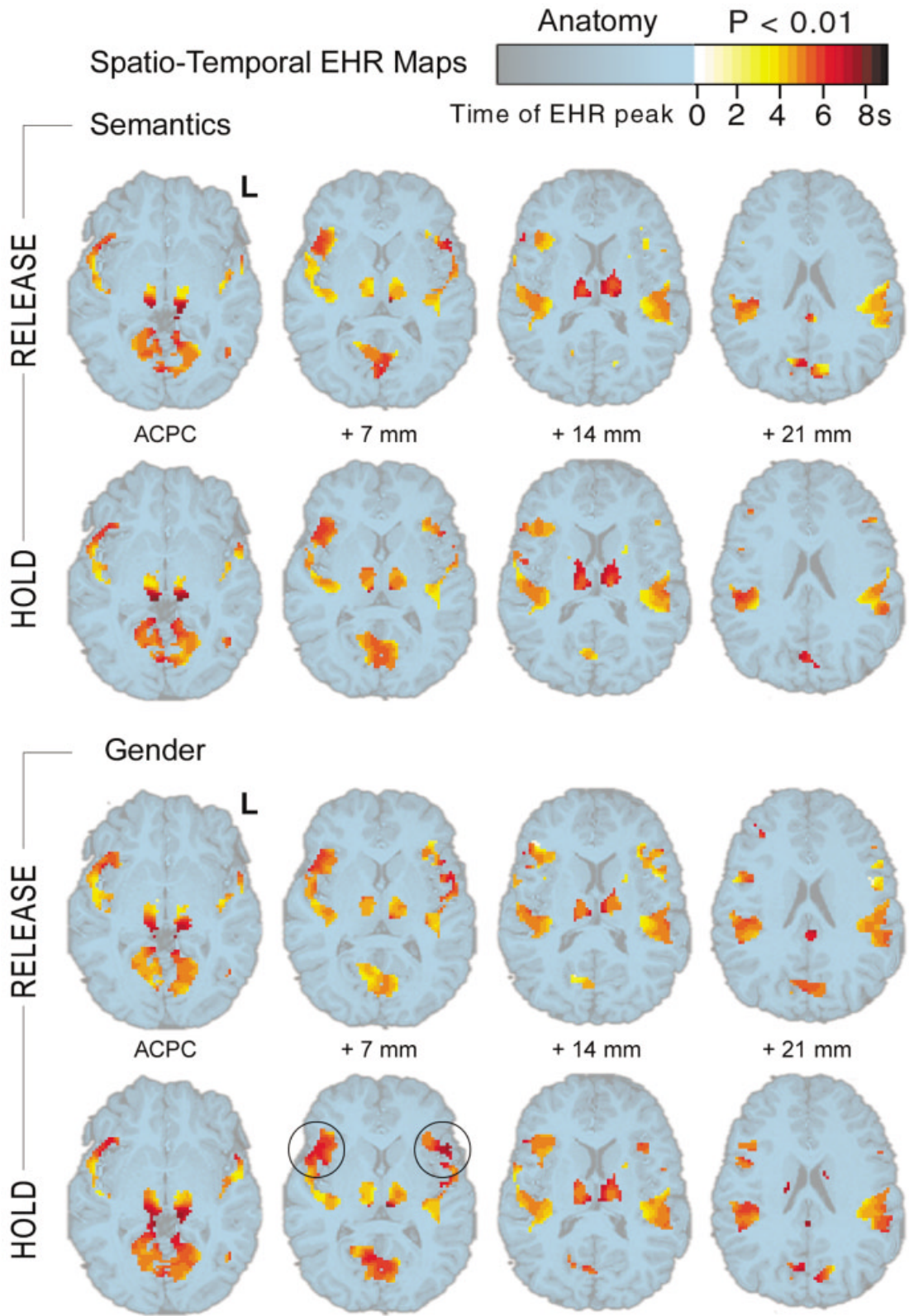


Figure 2.

ference between Congruent-Incongruent and Congruent-Congruent RTs [$F(1,23) = 20.25, P = 0.0002$].

Evoked haemodynamic responses

Activations were strikingly similar in all conditions and revealed a wide bilateral network including the STG, IPC, thalami, cunei, and lingual gyri (Table I, Fig. 2). Across task comparisons yielded no significant differences.

The ANOVA on EHR peak latencies showed (1) a significant language task main effect ($F[1,9] = 8.67, P = 0.0164$), EHRs being delayed in Gender compared to Semantics; (2) a near threshold condition main effect ($F[1,9] = 4.803, P = 0.056$), EHRs peaking later in HOLD than RELEASE; (3) a highly significant region main effect ($F[1,9] = 25.24, P = 0.0007$), EHRs peaking later in the insula/IPC than in the STG; and (4) a significant condition * region interaction ($F[1,9] = 30.38, P = 0.0004$) showing that inferior prefrontal EHRs were clearly delayed in HOLD vs. RELEASE, whereas the STG was insensitive to condition change (Table II, Fig. 3). There was no main effect of hemisphere [$F[1,9] = 0.21, P = 0.657$] and none of the other interactions reached significance. Most delayed peaks were found in voxel $[-46, 14, 7]$ (Talairach co-ordinate) located in the pars opercularis of Broca’s area and contralateral voxel $[39, 8, 7]$.

DISCUSSION

Four main results were obtained: (1) RTs were faster in RELEASE than HOLD and in Gender RELEASE than Semantics RELEASE; (2) activation patterns were

TABLE II. Results of the Four-Way ANOVA Performed on EHR Peak Latencies

Effect or Interaction	F	P
Task	8.670	0.0164
Condition	4.803	0.0561
Region	25.237	0.0007
Hemisphere	0.211	0.6570
Task * condition	0.036	0.8535
Task * region	0.037	0.8526
Task * hemisphere	0.036	0.8532
Condition * region	30.381	0.0004
Condition * hemisphere	0.540	0.4810
Region * hemisphere	3.323	0.1017
Task * condition * region	0.010	0.9238
Task * condition * hemisphere	0.057	0.8163
Task * region * hemisphere	1.859	0.2059
Condition * region * hemisphere	2.002	0.1908
Task * condition * region * hemisphere	0.433	0.5271

remarkably similar across tasks and conditions; (3) a significant haemodynamic peak delay between HOLD and RELEASE was identified in the inferior prefrontal regions but not in the superior temporal regions and this effect did not interact with language task.

As expected, RTs were shorter for RELEASE than HOLD and within the RELEASE condition, for Gender than Semantics. Participants tended to respond faster in the gender task but made more errors, which reflects a mild speed/accuracy trade-off effect. Gender decision may be facilitated by the fact that gender is binary (a word is either masculine or feminine in French), hence faster reaction times in RELEASE. This is a metalinguistic task, however [Miceli et al. 2002], and as such it is likely to elicit more errors. Semantic categorization, on the other hand, is more “natural” but requires dealing with a fuzzier dichotomy. *Vin* (wine), for instance, designates an object that is manufactured but derived from natural components such as grapes. Semantic decisions are thus likely to be made after longer consideration than gender ones.

Activated regions evidenced by the fMRI experiment corresponded to a network of regions previously described in auditory word processing [Belin et al., 2000; Binder et al., 2000; Démonet et al., 1992, 1994; Perani et al., 1999; Price, 2000; Price et al., 1996]. The relative symmetry of the network was congruent with recent studies [Friederici et al., 2000; Moro et al., 2001; Ni et al., 2000] and conceptualizations [Hickok and Poeppel, 2000]. Activations in visual association areas (cuneus, lingual gyrus) have been reported before in language experiments with auditory input [Démonet et al., 1994; Giraud and Price, 2001; Giraud et al., 2000;

Figure 2.

Spatio-Temporal maps derived from SPM results and EHR peak analysis. Activations ($P < 0.01$ uncorrected) are plotted for each task and condition on the anatomy of one subject (in blue). Color other than blue indicates the time of the EHR peak for each activated voxel. Early peaking EHRs (peak between 3 and 4 sec after SOT) were recorded in primary auditory cortices ($[-34, -33, 14]$ and $[29, -33, 14]$ $P < 0.0001$) and dorso-median aspects of the thalamus ($[-7, -17, 7]$ and $[4, -21, 7]$ $P < 0.0001$). EHRs peaking after 6.5 s (i.e., most delayed ones) were found in the pulvinar ($[-10, -33, 0]$ and $[9, -34, 0]$ $P < 0.003$), Broca’s area ($[-42, 12, 7]$ $P < 0.005$) and homologous right regions ($[42, 12, 7]$ $P < 0.0001$). Significant differences were found in the temporal analysis of Haemodynamic responses. Circles highlight the significant delay for prefrontal responses in Gender HOLD versus Gender RELEASE. Note that Wernicke’s area showed no sensitivity to task or condition, as illustrated by invariant temporal clusters on the 14-mm slices.

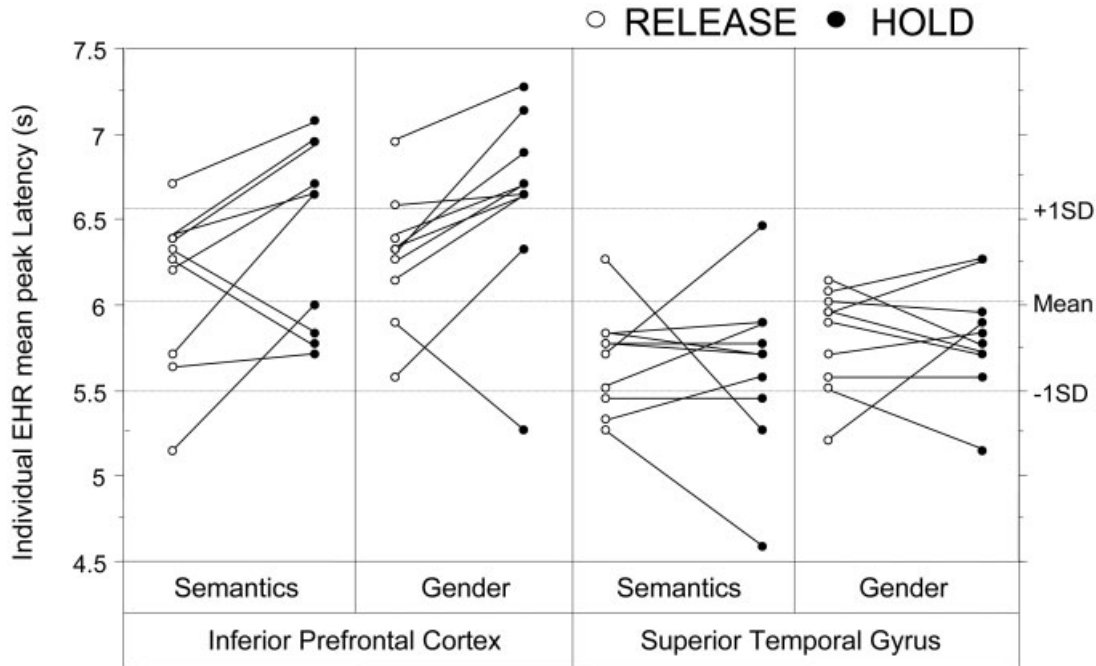


Figure 3.

Individual EHR peak latency plot for the IPC and the STG in both tasks and conditions. Individual EHRs were averaged in search volumes defined by coordinate intervals within Talairach space (see *Subjects and Methods*). Voxels included in the EHR analysis were activated at a threshold of $P < 0.01$ uncorrected. The line drawn between HOLD and RELEASE average EHR peak latencies shows the evolution from one condition to the other in each subject.

Zatorre et al., 1996] and in visual language tasks involving semantic and syntactic processing [Moro et al., 2001; Perani et al., 1999]. They may reflect visual mental imagery as a complementary strategy to carry out demanding tasks, especially in the context of the noisy environment created by the fMRI procedure. However, no anatomical difference was found across tasks or conditions. We assume that cognitive operations performed by participants were too similar across tasks to allow different neural networks to be involved. In particular, access to the meaning of words was most probably involved in both tasks.

The critical result of this study was a significant delay in the peaking latency of EHRs induced by the manipulation of the demand on VWM. The issue of haemodynamic responses variability has been addressed extensively in the last decade [Aguirre et al., 1998; Bandettini, 1999; Bandettini and Cox, 2000; Buckner et al., 1996, 1998; D’Esposito et al., 1999; Kim et al., 1997; Lee et al., 1995; Miezin et al., 2000; Schacter et al., 1997; Thierry et al., 1999]. Haemodynamic responses have been shown to be too variable across regions in terms of timing, amplitude, and shape for allowing direct comparison between different parts of the brain

[Bandettini, 1999; Buckner et al., 1996, 1998; Lee et al., 1995; Schacter et al., 1997]. Such regional differences might be due to variable influences of microscopic and macroscopic blood flow, to differential vascular sampling or real differences of neural activity [Buckner et al., 1998; Miezin et al., 2000; Schacter et al., 1997]. Although the haemodynamic response of one region is susceptible to be dysphased by several seconds across subjects [Buckner et al., 1998; Kim et al., 1997; Miezin et al., 2000], it has been proposed that its grand-average latency and amplitude are reliable for groups of subjects as small as $n=6$, i.e., the central tendency of the EHR can be reproduced in different groups of subjects and, a fortiori, in the same group of subjects with a precision of tenths of seconds [Buckner et al., 1998].

Here, we found that the mean EHR peak was significantly delayed by condition change in one region (the IPC) but not another (the STG). According to Miezin et al. [2000], the haemodynamic response in a given region is nearly identical from one data set to another (time to peak correlation $r^2 = 0.95$ across sets), therefore the significant difference found for the IPC can only relate to the difference introduced by condi-

tion or task variations. The STG, on the other hand, showed no sensitivity to condition change. Thus, the observed pattern cannot be the result of an overall inertia effect of blood flow in the brain [Thierry et al., 1999] but is rather a region-specific effect relating to condition-specific requirements.

Two different sources of modulation might explain the EHR delay in the IPC: (1) gender processing as opposed to semantic processing (involving left frontal regions [Caplan and Waters, 1999] and right prefrontal regions [Friederici et al., 2000; Ni et al., 2000]); and (2) VWM demands [Caplan and Waters, 1999; Paulesu et al., 1993]. Although Gender EHRs peaked later than Semantic EHRs overall (i.e., in both conditions and all regions), the task factor did not interact with the condition * region interaction. In Figure 3, an inferior prefrontal haemodynamic delay can be observed in HOLD vs. RELEASE for 8 subjects out of 10 in Semantics and 9 subjects out of 10 in Gender while no such global trend can be observed in the STG. In the absence of an interaction involving VWM condition, brain region, and language task, it appears that the major factor influencing the time course of the IPC haemodynamic response is VWM involvement rather than the linguistic task in question.

In sum, our results are congruent with other studies by showing that VWM demands differentially involve the IPC [Caplan et al., 2000]. Moreover, this region shows this trend of sensitivity for both gender categorization [Miceli et al., 2002] and semantic processing [Dapretto and Bookheimer, 1999], possibly because semantic selection, which involves VWM, is required [Thompson-Schill et al., 1997]. When semantic and grammatical tasks are highly comparable, there is no evidence for a separate spatial encapsulation, possibly because of the spatial resolution of 1.5 T fMRI. Finally, this study demonstrates that varying cognitive demands can selectively influence the time-course of haemodynamic responses in circumscribed regions of the brain.

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