



The anatomy and time course of semantic priming investigated by fMRI and ERPs

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Abstract

We combined complementary non-invasive brain imaging techniques with behavioural measures to investigate the anatomy and time course of brain activity associated with semantic priming in a lexical-decision task. Participants viewed pairs of stimuli, and decided whether the second item was a real word or not. There were two variables, the semantic relationship between the prime and the target (related or unrelated) and the interval between the onset of prime and target (200 or 1000 ms), to vary the degree of semantic expectancy that was possible during task performance. Behavioural results replicated the well-established finding that identification of the target is facilitated by a preceding semantically related prime. Event-related functional magnetic resonance imaging (efMRI) identified two brain areas involved in the semantic-priming effect. Activity in the anterior medial temporal cortex was diminished when target words were primed by semantically related words, suggesting involvement of this brain region during active semantic association or integration. In contrast, activity in the left supramarginal gyrus in the temporal-parietal junction was enhanced for target words primed by semantically related words. Brain areas influenced by the interval between prime and target words, and by the interaction between word interval and semantic priming were also identified. A parallel experiment using event-related potentials (ERPs) unveiled a striking difference in the time course of semantic priming as a function of expectancy. In line with previous reports, the primary effect of semantic priming on ERPs was the attenuation of the N400 component, in both short- and long-interval conditions. However, the priming effect started significantly earlier in the long-interval condition. Activity in the anterior medial temporal cortex has previously been shown to contribute to the N400 component, a finding that links the priming results obtained with efMRI and ERP methods.

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1. Introduction

Semantic priming [63] is used as a technique to examine mental representations of word meanings and their interrelationships. The semantic-priming effect is a measured advantage in the reaction-time (RT) or accuracy to identify or categorise a target word when it is preceded by a semantically related prime word (e.g. dog-cat) compared to an unrelated prime (e.g. bread-cat). Typically, prime-target pairs are presented in the context of a lexical-decision task, in which the participant has to decide whether the target item is a real word or not. According to one influential model [71], at least three processes contribute to the semantic-priming effect. (1) The first process consists of the automatic spread-

ing of activation between related word representations [18]. This process is believed to have a brief time span, and to contribute predominantly when words are separated by short temporal intervals [69,82]. (2) Semantic expectancy is a well-established controlled process, where at longer intervals between words, participants can generate an expected cohort of semantically related or associated candidate words [69,82,92]. Semantic expectancies are also made more prominent by increasing the proportion of related word pairs [22,26]. (3) Controlled post-lexical processes of semantic matching can also facilitate lexical-decisions [3,53]. After the meaning of the target word has been accessed but before the lexical-decision process is complete, detection of a semantic relationship between prime and target words can bias the lexical-decision response. If the target bears a semantic relationship to the prime word, it must also be a word. Post-lexical matching processes can contribute when intervals between words are either short or long.

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Studies using brain-imaging methods with high spatial resolution (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) have suggested that semantic representations and processing are selectively distributed [15,21,57,58,65]. In addition, some brain areas may provide functions that are of general use during semantic analysis [86,91,99]. For example, the inferior prefrontal cortex (BA 45/47) is often activated during semantic tasks [80], and has been suggested to perform an executive role during selection or retrieval of semantic information [31,87]. The anterior medial temporal cortex has also proved to play a critical role in semantic processing. Direct recordings from this region show word-related activity that is sensitive to both the semantic content and context of words [73,76]. Brain imaging studies have reliably shown activation here during active tasks of semantic association or integration [21,65,86,98]. Furthermore, damage to this area can lead to severe and generalised semantic impairments [37,66,67].

Semantic priming provides a highly controlled technique to isolate brain areas that are sensitive to semantic processes. However, running effective studies of semantic priming with imaging methods that required epoch-based experimental designs has been challenging. Consequently, only a few studies of semantic priming have been reported using PET [68] or blocked-design fMRI [89]. Mummery and her colleagues [68] measured the effects of semantic priming using PET by varying systematically the proportion of related prime and target words in a parametric design. They showed changes in activation in the left anterior temporal cortex, anterior cingulate, right superior parietal lobule and right premotor cortex, and interpreted only the temporal focus to be directly related to lexical/semantic processing. Based on prior literature, they suggested that the other brain areas participated in attentional aspects of task performance, which also increased with the proportion of related word pairs. Rossell and her colleagues [89] used fMRI to contrast (1) lexical-decision tasks containing semantic priming versus control tasks without semantic priming, and (2) semantic-priming conditions during lexical-decision with short or long intervals between word presentation. A distributed network of brain areas was involved during the lexical-decision task, including the left anterior temporal cortex and the anterior cingulate cortex. In addition, they found cingulate areas to be sensitive to the length of the interval between words. Both these studies provide a starting point for the investigation of semantic priming, but they lack the temporal resolution necessary to measure the brain activations specific to single types of trials during lexical-decision tasks. Blocked-design methods cannot dissociate the brain areas that are involved in on-line semantic processing (and modulated transiently by the semantic relationship between word pairs) from those that participate in tonic cognitive functions that are not sensitive to semantic context per se (e.g. strategies or attention).

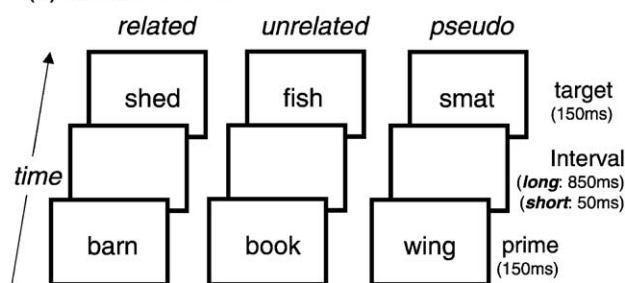
Event-related potentials (ERPs) provide an alternative means to measure brain activity non-invasively, yielding complementary information with high temporal resolution

but low anatomical resolution. ERPs have been extensively used to study dynamic language processes, and semantic analysis in particular [32,50,51]. The N400 component [47,49] is a negative component of the ERP waveform peaking between 300 and 500 ms, which has been repeatedly shown to be sensitive to semantic variables. For instance, semantic priming significantly attenuates the N400 [2,7,8,23–25,39,42,46,59,75,103] and controlled processes such as semantic expectancies have been shown to enhance this effect [6,13,14,17,38,93].

In the present study, we conducted parallel experiments with event-related fMRI (efMRI) and ERPs to investigate the

Semantic-Priming Task

(a) task conditions



(b) reaction-time data

	SOA	ERP subjects	fMRI subjects
Related	Short	760.8 (135.3)	659.1 (130.4)
	Long	771.1 (102.0)	680.9 (114.1)
Unrelated	Short	807.1 (147.3)	696.2 (126.6)
	Long	811.2 (108.8)	702.4 (115.7)

(c) behavioural results

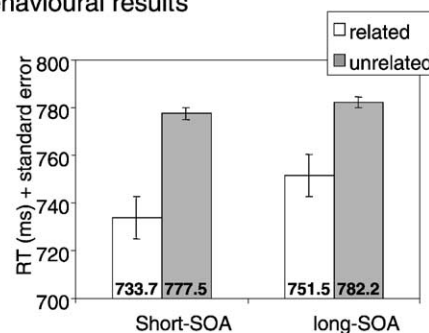


Fig. 1. (a) *Task schematic*: Participants completed two conditions of a semantic-priming lexical-decision task, which differed only in the interval between the prime and target stimuli. In the short-SOA condition, the interval between prime and target was 50 ms (200 ms SOA). In the long-SOA condition, the interval between prime and target was 850 ms (1000 ms SOA). In both SOA conditions, prime words were followed by one of three types of targets: related words, unrelated words or pseudo words. Participants indicated whether the target was a real word or not by using the index and middle finger of their right hand respectively; (b) *Reaction-time data*: A summary of the mean RT and standard deviations for related and unrelated word pairs at both SOAs, for both groups of subjects; (c) *Behavioural results summary*: Mean RT and standard errors for related and unrelated target words in the short- and long-SOA conditions averaged over both groups of subjects.

anatomy and time course of brain activity associated with semantic priming in a lexical-decision task. We used two experimental conditions (Fig. 1a), with short and long intervals between prime and target items, in order to manipulate the degree of semantic expectancies that could contribute to the semantic-priming effect. Event-related fMRI provided accurate anatomical information regarding the brain regions involved during single trial types in the different priming conditions. ERPs measured brain activity with real-time resolution, providing a sensitive measure of dynamic transient changes in neural processing of target words under different priming conditions.

Previous ERP experiments have compared the effects of semantic priming when prime and target words were separated by short and long intervals [2,11,25,39]. In all cases, the primary effects reported occurred on the N400 component. Semantic priming attenuated the N400 component elicited by visual words at both short and long intervals, but word interval did not significantly affect the N400 modulation. To unveil any additional effect of semantic priming upon ERPs, or any possible effect of word interval on semantic priming, we used a dense array of electrodes and a more wide-ranging statistical analysis strategy. In order to exploit fully the high temporal resolution of ERPs, we did not confine the statistical analysis to the N400 or to long time windows. In addition to standard analyses of ERP components, we compared brain activity in successive 20-ms time bins at different regions of the scalp in order to track the time course and distribution of brain activity linked to semantic priming.

2. Methods

2.1. Subjects

Two groups of subjects were tested to investigate the neural basis of semantic priming using efMRI and ERPs. It was not possible to study the same subjects with both methodologies because of constraints in the number of word stimuli available (see below). Repetition of stimulus material would have introduced additional confounding memory functions and practice effects during the tasks. In total, 30 subjects participated. All participants were right-handed (Edinburgh Inventory [77]), had normal or corrected visual acuity, and had no history of neurological disorders. Eight subjects were included in the efMRI experiment (4 males), between 19 and 30 years of age (mean 23 years). Twenty-two subjects were included in the ERP experiment (12 males), between 20 and 29 years of age (mean 23 years).

2.2. Semantic-priming task

The stimuli were 500 concrete nouns and 100 pseudo-words. They were arranged into 300 prime-target pairs, 200 pairs had semantically related words and 100 had words fol-

lowed by pseudo-words. Semantically related pairs were related by virtue of being co-exemplars of a given category (e.g. *lemon-pear*) rather than associative relationships (e.g. *key-lock*) as associative relationships are less 'pure' and can increase the degree of priming (see Neely [70] for discussion). These semantically related pairs were formed using category norms from Battig and Montague [4] and McEvoy and Nelson [61]. All words were nouns, four to six letters long, with frequency of 1–200 per million words and imageability ratings greater than 400 (MRC Psycholinguistic database). Pseudo-words were pronounceable and legally spelled letter strings (e.g. *pont*), constructed from permutations of 100 randomly chosen targets.

The stimuli were divided into two shorter lists (Lists 1 and 2) of 100 semantically related word pairs and 50 word-pseudo-word pairs (pseudo). Each list had an A and B version. In version A, 50 word pairs maintained their semantic relationship (related), while the pairing of the remaining 50 was re-arranged so that they now formed unrelated word pairs (unrelated). In version B, these relationships were counterbalanced, so that related pairs were now randomly re-assigned to create unrelated pairs, and the unrelated pairs were correctly assigned to their related word pairing. In addition, 50 "null-event" trials (null) were introduced into each shorter list. In these null trials only a fixation point was presented during the entire trial duration. The null trials provided a baseline condition during the efMRI experiment, and were also included in the ERP experiment for consistency. Each final list therefore contained 50 trials of four types: *related*, *unrelated*, *pseudo*, and *null*. The ordering of the trials was randomised in each list, with the constraint that any given trial type could not occur more than three times successively. During the ERP experiment only, the word BLINK was presented centrally every four trials, providing a 4 s window for blinks and eye movements.

Each subject completed two task conditions, which only differed in the timing of stimulus presentation (see Fig. 1). Subjects initially fixated on a central cross for either 50 or 850 ms, with an additional randomly assigned jitter of 0–300 ms (the jitter was for distributed sampling of the hemodynamic response in the fMRI task). This was followed by the centrally presented prime for 150 ms. After a short (50 ms) or long (850 ms) interval a central target appeared for 150 ms. Subjects were instructed to decide whether the target was a real word (i.e. an entry in the English dictionary) or a pseudo-word by pressing the left or right key of a response pad under their right hand respectively (within a 2500 ms response window). For both task conditions the total trial length was 3700 ms (with a 0–300 ms jitter). Assignment of list (1 or 2) to SOA condition, list versions (A or B), and the order of condition (long or short SOA) were all fully counterbalanced across subjects.

The behavioural effects of semantic priming during *short-* and *long*-SOA conditions were assessed using a

repeated-measures analysis of variance (ANOVA). The analysis concentrated on word pairs, and tested the effects of semantic priming (*related*, *unrelated*) and of SOA (*short*, *long*).

2.3. Event-related fMRI

Participants lay supine in the MRI scanner. Stimuli were back-projected onto a semi-opaque screen placed 30 cm in front of them. Participants viewed the display via tilted mirrors placed above their eyes, and responded using an MRI-compatible response pad placed under their right hand.

Magnetic resonance images were obtained using a 2T Magnetom Vision whole-body system (Siemens, Erlangen, Germany). Functional measures sensitive to the blood-oxygenation level dependent (BOLD) contrast [52] were obtained using single-shot echoplanar T2*-weighted imaging (TE = 40 ms, TR = 3 s). Thirty-four axial slices (64 × 64 voxel matrix, with 3 mm³ resolution) covered the entire cortex. The cerebellum was not fully included in the image set. During each of two experimental runs one task condition was presented (*short* or *long* SOA) and 259 image sets were acquired. The first five sets of images were acquired in the absence of any task, and were used to allow the signal intensities to saturate. These images were subsequently discarded. Over the remaining 254 images (762 s), the four trial types were presented for a total of 200 trials (3.7 s per trial). The random jitter (0–300 ms) between trial onset ensured an effective sampling of the hemodynamic response function [41]. Structural magnetic resonance images were taken using a T1-weighted sequence (1 mm × 1 mm × 1.5 mm resolution).

Data were processed and analyzed using Statistical Parametric Mapping (SPM 99, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (Mathworks Inc., USA). To correct for the different acquisition times of each image in the time series, the signal measured in each slice was shifted relative to the acquisition of the middle slice using sinc interpolation in time. To correct for possible head movements, volumes were then realigned to the mean image and re-sliced using a sinc interpolation in space. The T1 structural volume was also co-registered with the mean realigned EPI volume, to enable correspondence between functional activations and individual neuroanatomy. All images were subsequently spatially transformed into the stereotactic space of Talairach and Tournoux [95], using the averaged-brain template of the Montreal Neurological Institute. Functional images were spatially smoothed using an isotropic Gaussian kernel of 8 mm at full-width at half maximum (FWHM), so that the data conformed to a Gaussian model and to accommodate for inter-subject anatomical variability.

The hemodynamic response triggered by the target stimulus (i.e. event) in each trial-type and condition was modelled with two basis functions. These functions were a

canonical hemodynamic response function (HRF) [33], and a delayed HRF, shifted 3 s later in time (i.e. by one TR). These functions were used as covariates in a general linear model, together with a constant term for each participant. The data were high-pass filtered using a 150 s cycle, in order to eliminate artifactual sources of slow drift signals. Both the data and the model were temporally smoothed using a 4 s Gaussian kernel, to reduce temporal autocorrelations between images, and to account for the hemodynamic lag.

Statistical effects of the two experimental factors and their interaction were estimated using linear contrasts in fixed-effects analyses of variance according to the general linear model applied to each voxel in brain space [34]. Statistical parametric maps of the *t* statistic over voxels of brain images were generated and transformed into maps of the corresponding *z*-values. The resulting foci of activations were characterized in both peak height and spatial extent.

Four different effects were identified:

- (1) Main effects over all types of word targets in both SOA conditions (*short/related* and *short/unrelated* and *long/related* and *long/unrelated*) were identified relative to the null events.
- (2) Brain areas sensitive to semantic priming were investigated by contrasting *unrelated* and *related* targets in both the *short*- and *long*-SOA conditions. A conjunction approach [85] was used to identify consistent results in the two SOA conditions. For example, words preferentially activated by unrelated word pairs were calculated as the conjunction of ((*short/unrelated*–*short/related*) and (*long/unrelated*–*long/related*)). To rule out contributions from changes in relative deactivations, effects are only reported if there was also an effect of unrelated words relative to null events. This was achieved by using the inclusive-masking option in SPM ($P < 0.05$ uncorrected). The masking procedure also substantially decreased the probability of false positives by searching for effects only within regions defined *a priori* by the significant activations of the relevant trial types. Words preferentially activated by related words were calculated as ((*short/related*–*short/unrelated*) and (*long/related*–*long/unrelated*), masked by (*short/related*–*null events* and *long/related*–*null events*)).
- (3) Brain areas sensitive to SOA conditions were identified in an analogous fashion, using conjunctions of *short*- and *long*-SOA conditions for *unrelated* and *related* conditions: ((*long/unrelated*–*short/unrelated*) and (*long/related*–*short/related*), masked by (*long/unrelated*–*null events* and *long/related*–*null events*)) and ((*short/unrelated*–*long/unrelated*) and (*short/related*–*long/related*), masked by (*short/unrelated*–*null events* and *short/related*–*null events*)).
- (4) Brain regions corresponding to the four possible tails of the interaction (specific to *long/unrelated*, specific to *short/unrelated*, specific to *long/related* and specific to *short/related*) were segregated by masking the inter-

action with the effects of (a) one condition (e.g. *long/unrelated*) relative to null events; and (b) the effect of priming specific to an SOA (e.g. *long/unrelated–long/related*) (both at $P < 0.05$ uncorrected). For example, to identify the areas specific to long unrelated, the interaction (*(long/unrelated–long/related) > (short/unrelated–short/related)*), was masked inclusively by (*long/unrelated–long/related*) and by (*long/unrelated–null events*)).

3. Event-related potentials

Subjects were comfortably seated in a dimly illuminated and electrically shielded room, facing a computer monitor 100 cm away. Electroencephalographic activity (EEG) was recorded continuously from 54 scalp sites using non-polarizable tin electrodes mounted on an elastic cap (Electro-cap Inc.) and positioned according to the 10–20 International system. Recording sites included 8 midline electrodes (FPZ, FZ, FCZ, CZ, CPZ, PZ, POZ, OZ) and 23 electrodes over each hemisphere (FP1/FP2, AF3/AF4, AF7/AF8, F3/F4, F5/F6, F7/F8, FC1/FC2, FC3/FC4, FC5/FC6, FT7/FT8, C3/C4, C5/C6, T7/T8, CP1/CP2, CP3/CP4, CP5/CP6, TP7/TP8, P3/P4, P5/P6, P7/P8, PO3/PO4, PO7/PO8, O1/O2). The EEG was referenced to the right mastoid and then re-referenced offline to the algebraic average of the right and left mastoids. The midline electrode between FPZ and FZ served as the ground electrode. Electrooculogram (EOG) signals were measured bipolarly. Electrodes placed to the side of each eye measured the horizontal EOG, and electrodes above and below the left eye measure the vertical EOG. The signals were amplified 20,000 \times and digitised at a sampling rate of 250 Hz. Data were recorded with a band-pass filter of 0.03–100 Hz. Digital codes were sent from the stimulus-presentation computer to mark the onset and type of each target stimulus. In addition, codes were also sent to mark the “onset” of the target time during null-event trials.

The EEG was segmented off-line into epochs starting 1200 ms before and ending 824 ms after each target stimulus. Event-related brain potentials were created by averaging together trials of the same type. ERPs to *null* targets were also calculated. A period prior to target presentation was used to normalize the onset voltage of the ERP waveform. The baseline period for the long-SOA condition was between –100 and 0 ms before target presentation. The baseline for the short-SOA condition was between –300 and –200 ms before target presentation (i.e. 100 ms before the prime). Trials with eye blinks were eliminated, in which the voltage exceeded $\pm 50 \mu\text{V}$ at the horizontal or vertical EOG. Epochs containing large drift or amplifier blocking were also eliminated, in which the voltage exceeded $\pm 100 \mu\text{V}$ at any electrode site. Finally, trials with incorrect behavioural responses were also excluded. Subjects were discarded if there remained fewer than 22 trials in any condition.

Features of the ERP waveforms were analysed using repeated-measures ANOVAs, testing for the effect of semantic *priming* and its interaction with factors relating to the location of the recording sites. Because of the different shapes for the ERPs in the *long*- and *short*-SOA conditions, ERPs from these two experimental conditions were analysed separately. The Greenhouse–Geisser epsilon correction factor was applied to account for possible effects of non-sphericity where appropriate [40]. Only corrected probability values and degrees of freedom are reported.

The main ERP component implicated in semantic priming to date is the N400. The effect of semantic *priming* on the N400 was measured between 300–500 ms across midline and central sites using nine electrodes (F3/FZ/F4, C3/CZ/C4, P3/PZ/P4). The electrode locations were subdivided into three regions (left hemisphere, midline and right hemisphere). The resulting factors in the ANOVA were: *priming (related, unrelated)*, *region (left, midline, right)*, *electrode site (frontal, central, parietal scalp)*. The P300 component was measured between 500 and 700 ms using the same electrode sites and statistical factors. These analyses were based on previous literature (i.e. the N400 and P300 are commonly analysed at these electrodes, over these time periods) (e.g. for electrode locations see [100], and for time periods see [45,48]).

In addition to the standard N400 and P300 analyses, we adopted additional exploratory analyses to search for any other possible localised differences in ERPs due to semantic priming. This approach also examined the onset time of significant priming effects, with a 20 ms resolution. Successive mean voltage values (mean amplitude) every 20 ms between 0 and 600 ms after target onset were used as dependent variables in five regional analyses (midline, frontal, lateral, central and posterior). Each region contained five electrode sites in each hemisphere. The frontal analysis included sites: FP1/2, AF3/4, F3/4, F5/6 and F7/8. The midline analysis included sites: FCZ, CZ, CPZ, PZ, POZ and OZ. The lateral analysis included sites: FC5/6, FT7/8, C5/6, T7/8 and CP5/6. The central analysis included sites FC1/2, FC3/4, C3/4, CP1/2 and CP3/4. The posterior analysis included sites: P5/6, P7/8, PO3/4, PO7/8 and O1/2. Overall, the regional analyses sampled experimental effects over all the sites over the scalp. Three factors were tested at each SOA using within-subjects ANOVAs: *priming (related, unrelated)*, *hemisphere (right, left)* and *electrode location (five sites)*. *Hemisphere* was not relevant in the midline region. To compare effects of semantic priming across different SOAs directly, regional ANOVAs were also conducted with semantic-priming subtraction waveforms (*unrelated–related*) using SOA (short, long) as a within-subjects variable. Because of the risk of false-positive effects in the multiple interrelated comparisons in the regional analyses, results were only considered significant if they persisted over at least two successive time bins in a given region (i.e. >40 ms).

4. Results

4.1. Behavioural effects

Accuracy of the lexical-decision response was very high for both related and unrelated word pairs at both SOAs (<3.5% errors). Thus, subsequent analysis concentrated on the reaction-time (RT) data. Incorrect responses were excluded from the analyses. Responses that were unusually fast, <200 ms, or slow, >2000 ms, were considered errors and also excluded. Priming was calculated as the difference in mean RT between semantically *unrelated* and *related* trials.

Analysis of the RTs showed that the 22 ERP lab participants were significantly faster to respond to targets preceded by semantically related words, as shown by a main effect of semantic *priming* ($F(1, 21) = 140.6$ $P < 0.001$). There was no main effect of SOA condition ($P = 0.63$), however, *priming* and SOA interacted significantly ($F(1, 21) = 7.8$, $P < 0.01$). Planned contrasts (paired t -tests), comparing each condition relative to all others, established that there were significant effects of *priming* at both SOAs (short: $t(1, 21) = 10.2$, $P < 0.001$, long: $t(1, 21) = 9.85$, $P < 0.001$), but the *priming* effect at the short SOA was larger (46 ms) than the *priming* effect at the long SOA (34 ms). Analysis of the reaction-time data for the eight fMRI subjects showed exactly the same pattern of results. There was a main effect of priming ($F(1, 7) = 59.6$ $P < 0.001$), no main effect of SOA ($F(1, 7) = 0.81$ $P < 0.39$) and a priming \times SOA interaction ($F(1, 7) = 3.01$ $P < 0.05$). Priming was significant at both SOAs (short: $t(1, 7) = 4.9$ $P < 0.002$, long: $t(1, 7) = 6.1$ $P < 0.001$), with again larger priming at the short (37 ms) versus the long SOA (21 ms). Fig. 1b and c summarise this consistent pattern of results.

4.2. Brain activations

Many brain areas were activated by word recognition during the lexical-decision tasks (see Table 1). Activations occurred in brain regions consistently reported to participate in networks of word recognition. The visually presented stimuli resulted in marked bilateral activation of ventral occipital, occipital pole and occipitotemporal cortices. The peak of the activation occurred around the posterior fusiform gyrus (see [73]). The activations were extensive, and included the left posterior basal temporal area implicated in word naming [83]. Despite the reported problems with obtaining reliable fMRI signals from some lateral temporal areas (see [27,102]), target words activated foci in the middle and posterior left superior temporal gyrus, and in posterior right middle temporal gyrus. Frontal activations occurred bilaterally in inferior frontal gyrus (BA 47) and in premotor cortex (BA 6/44), and medially in the premotor cortex (BA 6). An additional activation occurred in the right ventrolateral prefrontal cortex (BA 45/46). Parietal activations occurred bilaterally in the superior parietal lobules (BA 7) and in the

Table 1

Peak coordinates (Talairach and Tournoux, 1988) and z -scores for activations during lexical-decision on unrelated and related word pairs at both SOAs

Region	X Y Z (mm)	z -score
Occipital and occipito-temporal		
L ventral occipital and occipitotemporal	−44 −64 −12	6.59
R ventral occipital and occipitotemporal	+22 −52 −20	5.80
L occipital pole	−28 −94 −06	4.02
R occipital pole	+22 −90 −10	3.83
Temporal		
L superior temporal gyrus	−54 −26 +20	4.64
	−56 −44 +20	4.12
R middle temporal gyrus	+64 −40 +04	4.91
	+54 −68 +05	4.75
Frontal		
L inferior frontal gyrus (BA 47)	−52 +16 +00	4.12
R inferior frontal gyrus (BA 47)	+52 +22 −04	3.63
L premotor (BA 6)	−48 +04 +32	3.62
R premotor/prefrontal (BA 6/44)	+50 +12 +36	4.06
R ventrolateral prefrontal (BA 45/46)	+56 +36 +18	4.49
Medial premotor (BA 6)	+06 +20 +46	3.48
Parietal		
L postcentral gyrus	−38 −26 +54	4.84
L superior parietal lobule (BA 7)	−20 −64 +56	4.47
R superior parietal lobule (BA 7)	+32 −60 +50	3.89
Subcortical		
Medial cerebellum	+02 −60 −22	3.88
L thalamus	−12 −18 +06	3.83

left postcentral gyrus near the central sulcus. The latter focus is consistent with activation of the hand sensory/motor area, related to the execution of right-handed responses. Subcortically, activation was obtained in the left thalamus and in the medial cerebellum. The cerebellum was not sampled completely, so other activations in this structure could have been missed.

Table 2

Peak coordinates (Talairach and Tournoux [95]) and z -scores for brain areas that show modulation by the experimental factors of semantic priming and SOA

Region	X Y Z (mm)	z -score
Unrelated – related pairs		
L anterior medial temporal	−40 +14 −34	3.60
Related – unrelated pairs		
L supramarginal gyrus (BA40)	−50 −40 +36	4.31
Long – short SOA		
Anterior cingulate gyrus (BA 24/32)	−02 +38 +16	3.85
Short – long SOA		
Visual cortex (calcarine area)	+16 −82 +00	3.97
Lateral occipital gyri	−28 −82 +12	4.00
	+42 −78 +00	3.57
L fusiform (medial temporal/occipital)	−32 −38 −28	3.69
L lateral cerebellum	−40 −60 −36	3.43
Interaction between priming and SOA		
R posterior superior temporal gyrus/supramarginal gyrus (BA 22/40)	+56 −46 +30	3.93

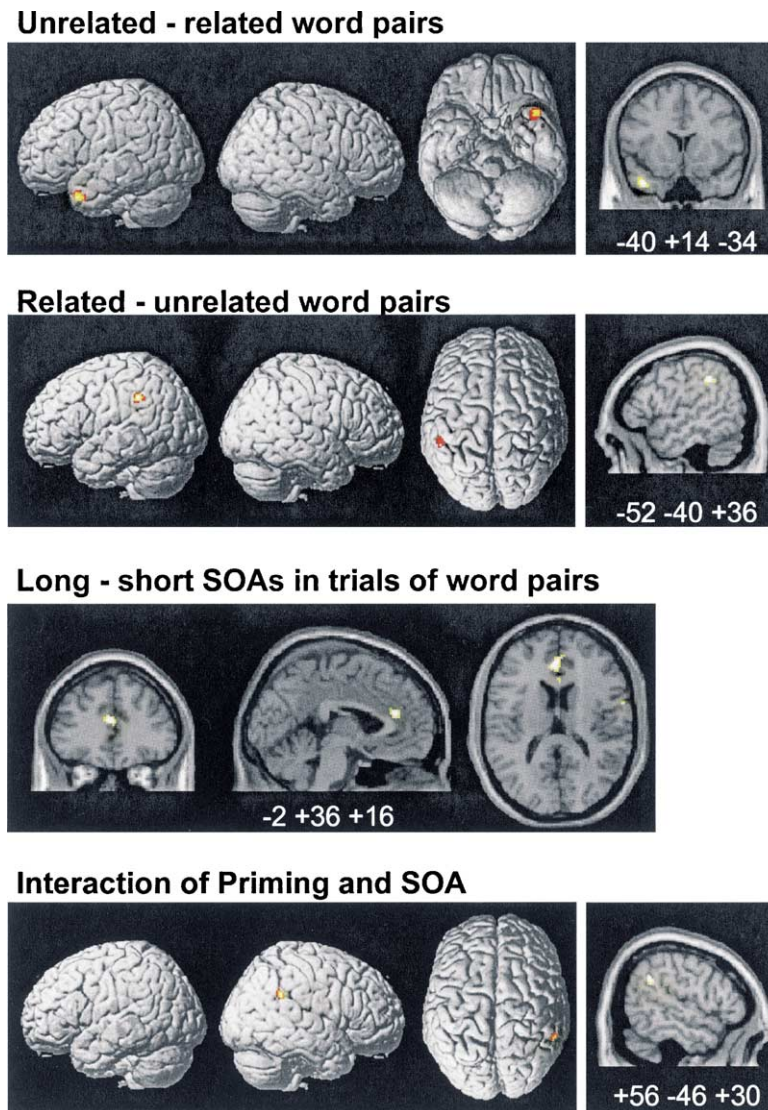


Fig. 2. Brain areas modulated by semantic priming (top two rows), (b) SOA (third row), and their interaction (bottom row). Activations are displayed from multiple perspectives on a surface rendering of a typical brain, and/or on brain sections, in order to facilitate anatomical localisation.

Semantic priming had clear effects on brain activations (Table 2 and Fig. 2). Activation in the left anterior medial temporal cortex was diminished in semantically related targets (unrelated–related), whereas activation in the left supramarginal gyrus of the inferior parietal cortex was enhanced in semantically related targets (related–unrelated).

The SOA between prime and target word stimuli also had significant impact on brain activations (Table 2 and Fig. 2). Trials with long SOAs preferentially activated the anterior cingulate cortex. Trials with short SOAs preferentially activated several visual foci and the left lateral cerebellum.

One brain region showed an interaction between *priming* and SOA. A focus in the right temporal parietal junction was more sensitive to priming (unrelated–related targets) during the long SOA condition than the short SOA condition. Specifically, the activation occurred in the posterior portion of the right superior temporal gyrus, at the junction with the

supramarginal gyrus. No brain area was more activated by priming during the short SOA condition than the long SOA condition.

4.3. Event-related potentials

After rejection of trials with artifacts or response errors, a comparable number of trials remained in the average ERP per trial type in each subject (short/related = 40.2, short/unrelated = 39.2, long/related = 39.5, long/unrelated = 38.6). At long SOAs, the ERPs elicited by targets showed characteristic waveform topology, including earlier lateralised posterior visual responses (P1, N1), a prominent language-related N400 potential, and a late positive P300-like component. Fig. 3 shows grand-averaged waveforms elicited by targets in *related*, *unrelated*, and *null* trials from representative midline and lateral electrode

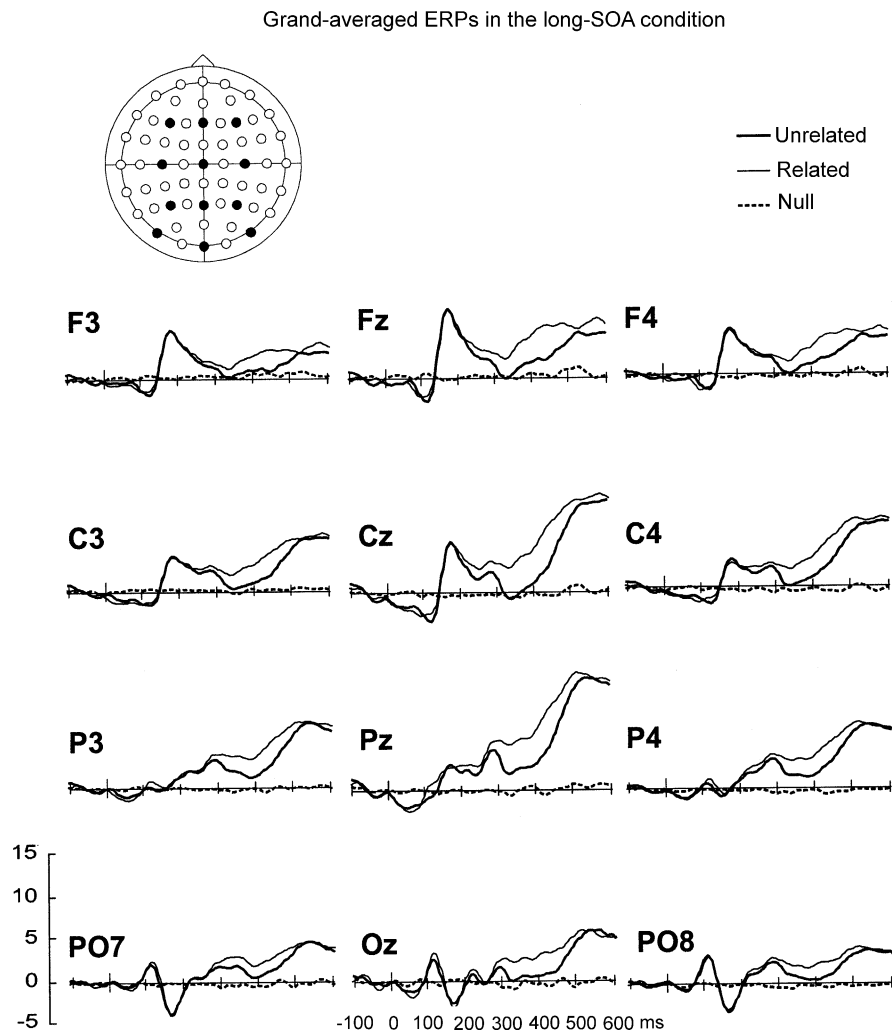


Fig. 3. Grand-averaged ERPs ($N = 22$ participants) obtained in the long-SOA condition at 12 representative electrode sites. A bird's eye view of the electrode montage is also shown, with the plotted electrodes shaded black. Scale bars on the bottom row of electrodes show the time course and the voltage range of the waveforms. Positive polarity is plotted upward. Waveforms elicited by targets in the unrelated (thick solid line) and related (thin solid line) word-pair conditions are compared. The N400 component and its modulation by semantic priming can be clearly seen. Also plotted is the activity elicited at the time there would have been targets during null-event trials (dashed line), validating this baseline condition in the efMRI experiment.

sites. As can be readily noted, no consistent brain activity was engaged during the null trials. At short SOAs, ERPs elicited by targets overlapped extensively with the ERPs of the preceding primes, making the identification of the visual potentials more difficult. At both SOAs it was possible to identify the N400 and P300 potentials.

Analysis of the N400 showed its attenuation by semantic priming during both *long-* ($F(1, 21) = 13.55$, $P = 0.001$) and *short-SOA* ($F(1, 21) = 8.27$, $P = 0.01$) conditions. In line with several previous reports, N400 was larger for semantically unrelated targets than for targets that were primed by a semantically related word. The effects were larger over central and parietal sites over the midline and right hemisphere. At long SOAs, the interaction between *priming* and *hemisphere* was significant ($F(1, 21) = 10.33$, $P = 0.001$),

and the interaction between *priming*, *hemisphere* and *electrode* approached significance ($F(2.7, 56.3) = 2.54$, $P = 0.07$). At short SOAs, the interaction between *priming* and *hemisphere* approached significance ($F(1, 21) = 3.01$, $P = 0.08$), and the interaction between *priming*, *hemisphere* and *electrode* was significant ($F(2.5, 52.2) = 4.08$, $P = 0.02$). For both SOAs the interaction of *priming* and *hemisphere* was the result of a larger effect over the midline and right hemisphere; and the 3-way interaction between *priming*, *hemisphere* and *electrode* the result of a larger effect over central sites (i.e. C4).

The P300 did not show any significant modulation during the long-SOA condition. At the short SOA condition, only the interaction between *priming* and *electrode* reached significance ($F(1.6, 33.8) = 3.38$, $P = 0.04$). The P300 was

larger for semantically related target words over the parietal electrodes.

Regional analyses over successive time periods determined the time course and distribution of the effects of semantic priming in *long*- and *short*-SOA conditions. They revealed that semantic priming influenced brain activity with a different time course in the two SOA conditions. Significant main effects of semantic *priming* started earlier for

targets in the *long*-SOA condition (300 ms) compared with the *short*-SOA condition (360 ms). The effects persisted continuously until 520 ms in both cases, and were observed over all scalp regions (all $F(1, 21) > 4.2$, $P < 0.05$).

Direct statistical comparisons of the subtraction waveforms (unrelated–related) for long and short SOA conditions separately established that the priming difference started significantly earlier and had greater mean amplitude for the

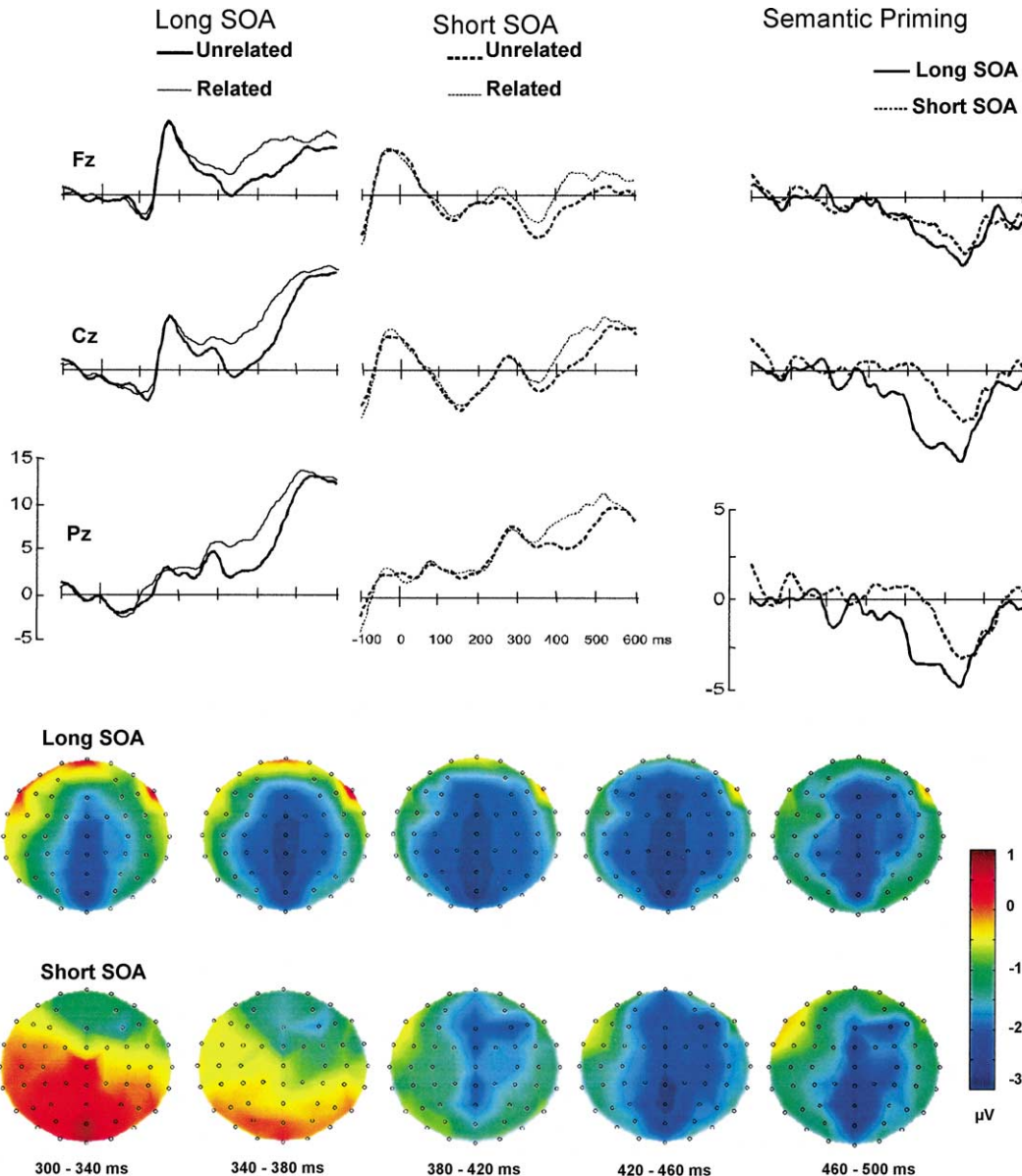


Fig. 4. Comparison of semantic-priming ERP effects at long and short SOAs. In the top panel, grand averaged ERPs are plotted at three representative midline electrodes for the unrelated (thick lines) and related (thin lines) target words in the long- (left column) and short-SOA (middle column) conditions. In the short-SOA condition, there is overlap from the ERPs elicited by the preceding prime words, making the identification of components elicited by the targets more difficult. The right column of the top panel shows a comparison of the semantic-priming effect isolated by subtraction waveforms (unrelated minus related targets) at the long- (solid lines) and short-SOA (dashed lines) conditions. The voltage range used for plotting the subtraction waveforms is different from those used to plot the original grand-averaged waveforms. The bottom panel contains the scalp distributions of the semantic-priming effect isolated by subtraction waveforms (unrelated minus related targets) at the long-SOA and short-SOA conditions, at successive 40 ms intervals between 300–500 ms. The voltage range, shown on the scale bar, is held constant to enable comparison of the magnitude as well as the distribution of the semantic-priming effect. The semantic-priming effect consists of the modulation of the N400 potential, and is significant earlier at the long-SOA condition (starting at 300 ms) than at the short-SOA condition (starting at 360 ms).

long-SOA compared to the short-SOA. The interaction of SOA \times electrode was significant in all five regions between 300 and 360 ms (all $F > 2.9$, $P < 0.05$). The differences were maximal centrally and at the midline, confirming that the directed N400 analysis examined this potential at adequate electrode sites. Fig. 4 shows the time course and distribution of the semantic-priming effect in *long*- and *short*-SOA conditions, with representative midline waveforms and scalp topographies.

Inspection of the subtraction waveforms also revealed an additional early negative component between 120 and 140 ms at the long SOA only. Examination of the topographies showed a midline–central distribution of this negativity, similar to that of the N400. The midline analysis comparing short and long SOAs showed a significant SOA \times electrode interaction at this time bin ($F(2.4, 49.4) = 4.19$, $P = 0.02$). The effect did not, however, fit into our criteria of persisting over two successive time bins. The effect may be robust despite its transient nature and merits further investigation.

5. Discussion

We used complementary brain imaging methods with high spatial and temporal resolution to identify the anatomy and time course of brain activity associated with semantic priming [63]. We also varied the SOA to examine possible contributions of semantic expectancy [70].

The behavioural results showed significant effects of semantic priming in the lexical-decision task, at both short and long prime-target intervals. The replication of the semantic-priming effects in the efMRI and ERP experiments showed that task performance was normal and consistent under these imaging conditions. The behavioural semantic-priming effect was consistently larger in the short-SOA condition compared to the long-SOA condition. One possible explanation for this behavioural finding is that facilitatory priming effects were fading by the end of the long 1000 ms SOA. A shorter SOA (e.g. 750 ms) may have been better to capture priming at its peak. However, without more extensive parametric variation of the SOA it is difficult to make strong claims about the time course of the contribution of the automatic and controlled processes to the semantic-priming RT effects.

The efMRI results revealed the sensitivity of left-hemisphere language areas to visual presentation of words. The ERP results replicated the well-established finding of attenuation of the N400 component by semantic priming. This effect started significantly earlier during the long-SOA condition compared to the short-SOA condition. Semantic expectancies were therefore found to enhance the time course of brain activity linked to certain aspects of semantic processing, despite the reduced effect of priming during the long-SOA condition observed at the behavioural level. One possibility for the dissociation between the behavioural and

the ERP findings is that the RT measure may be speed limited by overlapping processes (in a bottleneck type fashion), especially at the short SOA where there is very little temporal distance between the prime and the target, whereas with ERPs it is possible to follow information-processing on-line (see also [100] for further discussion).

5.1. Brain activations linked to semantic priming and expectancies

Unlike previous PET/fMRI studies, the effects of semantic priming were measured on a trial-by-trial basis. The hemodynamic responses were measured to targets that followed either semantically related or unrelated primes. Although these HRF responses reflect the activity of both prime and target words in a given trial type (since their close and systematic temporal proximity does not allow the disambiguation of their responses) prime stimuli were always of the same kind in all types of trials and therefore contribute a common source of activation. The only experimental variable, for each SOA condition, is therefore the semantic relationship that arises between targets and the preceding primes.

Semantic priming had clear and focal effects on brain activations. Activity in left anterior medial temporal cortex was significantly larger during the presentation of unrelated words compared to related words. In contrast, activity in the left supramarginal gyrus in the inferior parietal lobule was significantly larger during the presentation of related words compared to unrelated words.

The activation of the left anterior medial temporal cortex is consistent with the involvement of this area in semantic analysis of word stimuli. Intracranial recordings from the cortical surface have shown that brain activity in this region was diminished by semantic priming [35,36,60,73,76]. Similarly, brain-imaging studies using PET [68] and fMRI [89] also showed changes in activations in the left anterior medial temporal cortex during semantic priming. However, these studies measured brain activity during blocks of trials, and therefore were not able to dissociate changes in event-related activations that were directly linked to semantic priming, from tonic changes in brain activations caused by changes in attentional set. In these previous studies, other brain areas were also activated, and were tentatively interpreted as representing tonic attentional or state-related cognitive functions. The present results clarify the involvement of the left anterior medial temporal cortex in the transient effects of priming, and supports the interpretation that other areas reported during semantic priming may have reflected accompanying tonic cognitive functions. The left anterior medial temporal cortex has also been identified in other active tasks of semantic association [21,60,65,86,98,99]. Lesions of this brain area lead to general deficits in semantic processing, as observed clearly either after stroke [20] or semantic dementia [37,66,67]. Damasio has further suggested that medial temporal areas provide a critical mediating

function between word forms and the distributed representations of their meanings [20]. An alternative possibility, given the anatomical location of the area in the multimodal limbic cortex and near the hippocampus, is that the region provides a convergent network critical for the integration of words with their context or with ongoing linguistic discourse (see [97,98]). These associative representations may be important for the formation of semantic memories and may become integrated within episodic traces (see [30,64,101]).

The left supramarginal gyrus (SMG) in the inferior parietal lobule within the temporal parietal junction (BA 40) showed significantly enhanced activation during related word trials. Greater activation of this brain area during related than unrelated word pairs suggests a different kind of function during the lexical-decision task. Such activations may represent either automatic spreading of activation or post-lexical processes related to the detection of a semantic relationship between the words [53,70,71]. The SMG lies in associative and multimodal cortex [62]. Its activation has often been reported in language experiments, and has mainly been linked to processing of phonological information [9,10,86,91] and phonological working memory [78,84]. We speculate the SMG, is therefore, well suited as a site where information about semantic relationships can influence lexical-decisions about the phonological forms of words, or a site where rehearsal of related word representations can facilitate lexical-decisions.

Brain areas sensitive to the functions that contribute differentially to semantic priming at short- and long-SOA conditions were investigated by testing for the interaction between the *priming* and *SOA* factors. Only one area was sensitive to the differences in priming in the two SOA conditions—the right posterior superior temporal gyrus at the junction with the supramarginal gyrus (see also [89]). This area showed increased activation to the unrelated compared to related word-pair trials, for the long-SOA more than the short-SOA condition suggesting involvement of controlled processing. The functional significance of this activation is difficult to interpret. Rossell et al. [89] have speculated that this activation is a homologue of left hemisphere Wernicke's area, pointing to a number of studies that have demonstrated right hemisphere activation of posterior temporal regions during semantic tasks [12,43,44,94]. Also, neuropsychological studies using divided-visual field presentation have shown that lexical activation is slower in the right hemisphere [1,16]. Alternatively, the right temporal parietal junction could play a more strategic role, such as providing an attentional function. Damage to this brain region leads to hemispatial neglect [88], and its activation is observed in conditions that isolate spatial attentional factors (see [19,72]) including multimodal integration [28,55]. In this study, one possibility is that subjects detected more mismatch between cognitive semantic expectancies and the target words. This would represent a semantic analogue of what happens when a spatial target appears at the wrong location, a situation that also activates this brain

region [19,74]. The interpretation remains highly speculative, and directed research into attentional modulation of linguistic expectancies will be required to clarify the issue.

The differences in brain activation as a function of SOA that were independent of priming were also assessed. Long-SOA trials enabled the formation of cognitive expectancies about word meanings, and resulted in preferential activation of the anterior cingulate cortex. Activation of the anterior cingulate cortex has been reported previously during semantic-priming conditions that emphasise controlled processes including expectancies [68,89]. Activation during manipulations of expectancy but not of *priming* in the present task shows that previous activations were not specific to the semantic relationships between words, but instead reflected changes in controlled processes during different task conditions. Anterior cingulate activation has also commonly been reported in tasks that afford expectancies or controlled processing, both in the domain of language [79,80] and in other cognitive domains (see [81]). In contrast, short-SOA trials emphasize overlap of activations between word representations that are not sensitive to the semantic relationship between words, and may also invoke processes to resolve the temporal overlap between stimuli. Short-SOA trials resulted in the preferential activation of several visual areas and the left cerebellum.

5.2. The influence of expectancies on the time course of semantic priming

The primary effect of semantic priming on ERP waveforms was replicating attenuation of the N400 potential [7,24,38,46,75,90]. We did not observe any other reliable modulation of the ERP waveforms. However, the analysis of successive 20-ms time bins over the different regions of the scalp did reveal a striking difference between the onset of the N400 semantic-priming effect as a function of the SOA. This statistical approach enabled us to chart the onset and duration of significant effects of semantic priming on the N400 without relying on its peak amplitude, which can often be shifted by overlapping later positive components (see [6,24]). In the long-SOA condition, which afforded anticipatory semantic expectancies, the N400 effect was significant in the 300–320 ms time period and persisted until 520 ms. In contrast, for the short-SOA condition, the first significant effect occurred at 360–380 ms and also persisted until 520 ms. Statistical comparison between the subtraction waveforms, which isolated the effects of semantic priming at the *long-* and *short-SOA* conditions, confirmed the earlier onset of priming in the presence of semantic expectancies between 300–360 ms.¹

¹ It is equivocal whether the onset of the semantic priming effect is early in the long-SOA condition versus late in short SOA-condition. Our data merely shows a difference in the N400 onset between the two conditions, one earlier/late than the other.

Evidence from intracranial recordings provides a vital link between the ERP and efMRI effects of semantic priming. The anterior medial temporal cortex has been shown to contribute to the generation of the N400 component recorded at the scalp. Potentials elicited by word stimuli in this region have a similar time course to the N400 recorded from the scalp, and show an equivalent pattern of modulation by semantic content and context of words [35,36,73,76]. Furthermore, the potentials reverse in polarity between the neocortical surface and intracerebral locations, indicating their local generation [60,76]. Therefore, both the efMRI and ERP results plainly point to the involvement of the anterior medial temporal cortex during semantic analysis or integration of word stimuli. The ERP results further reveal that controlled semantic expectancies can influence the timing of semantic facilitation by a related context. Because of the very close temporal proximity between word stimuli relative to the long temporal function of the hemodynamic response, it was not possible to observe these relative changes in the time-course of anterior medial temporal activity (or elsewhere) with the fMRI method alone. The bridge between methodologies enables a much more complete interpretation of the changes in activation observed with efMRI.

According to most theoretical perspectives, the N400 reflects post-lexical semantic functions that can be influenced by controlled processes [13,39]. The N400 semantic-priming effect has been consistently shown to be sensitive to manipulations of semantic expectancies. For example, the N400 priming effect is larger when the proportion of related words is higher [14,38,93] and when subjects are instructed to develop semantic expectancies [5,38]. However, the possibility that N400 modulations can also reflect automatic processes of semantic access has not been completely excluded. N400 attenuation has also been reported during tasks that require only shallow analysis of the stimuli and semantic relationships that are incidental to task performance [8,42,46]. In some of these experiments, post-lexical semantic-matching processes may have contributed to the effects. In situations where the controlled semantic processes have been shown to be minimal or non-existent, N400 effects have not been obtained. For example, when subjects matched letter-case within words, behavioural semantic priming occurs but no N400 effect was obtained [17]. Similarly, when prime words are masked so that they are not consciously perceived, behavioral effects of semantic priming have been reported in the absence of N400 effects of semantic priming ([14], but see [23,54]).

The pattern of N400 attenuation we observed in the ERP experiment is therefore most compatible with the operation of controlled processes of semantic expectancies and post-lexical semantic matching. During the short-SOA condition, in which the effects of automatic spreading of activation should be most pronounced [82], the priming effect on the N400 started later. This would not be so if the N400 modulation reflected primarily automatic spreading of activation. At the long-SOA condition the earlier onset of the N400

effect most likely reflected facilitation of semantic processing by controlled expectancies. Post-lexical semantic matching may have also contributed to the N400 effects during both *long-* and *short-SOA* trials (see [45,100] for similar findings using sentence presentation at short and long SOAs).

Our findings extend previous ERP semantic-priming studies in which the SOA has been manipulated (e.g. [2,11,25,39]). Deacon and colleagues [25] found a marginal effect of SOA, in task conditions where subjects were instructed to associate two different semantic categories to build controlled expectancies (i.e. birds with body parts). The N400 effects were larger at long-SOA (2000 ms) compared to short-SOA (250 ms) conditions. No previous report, to our knowledge, shows a significant difference in the evolution of the semantic-priming effect over time as we have done; this may be due to differences in data acquisition or analysis strategy (cf. [14,45]). Yet, to completely establish the time course of semantic expectancy a range of SOAs must be used with a parametric design (as noted earlier with regard to our behavioural results).

The marked enhancement in the time course of controlled operations has not typically been reported in other cognitive domains. For example, selective spatial attention alters the magnitude but not the latency of potentials linked to visual perception and response selection for simple stimuli [29,56]. The enhancement of controlled semantic analysis would be particularly advantageous during on-line language processing, which places notorious demands on temporal integration mechanisms (e.g. [96]).

6. Conclusions

The main advances contributed by our present experiments on the neural basis of semantic priming are the increased temporal resolution and the bridging between methodologies. Using event-related fMRI we were able to separate modulations of brain activity that were specifically related to the processing of related and unrelated word pairs during a lexical-decision task from tonic changes in brain activity during blocks of predominantly related or unrelated word pairs [68,89]. We replicated the previous finding of decreased activation in the anterior medial temporal cortex as a function of semantic priming by a related word. In addition, our results helped clarify that other areas imaged during semantic priming in blocked-design tasks were unlikely to reflect semantic analysis per se. In particular, our results suggest that the anterior cingulate cortex may reflect general attentional processing rather than language-specific processes related to contextual facilitation of word recognition. We also speculate that left supramarginal gyrus activation may contribute a facilitatory function during semantic priming.

We also exploited the high inherent temporal resolution of the ERP methodology, and discovered that semantic expectancies afforded by longer intervals between prime and

target words enhances the time course of word recognition. The primary effect of semantic priming on ERP waveforms occurred on the N400 component, known to reflect activity in the anterior medial temporal cortex (e.g. [60]). Modulation of the N400 started significantly earlier in the long-SOA trials relative to the short-SOA trials. The extensive literature on the N400 modulation during semantic tasks, and our own results, suggest that the anterior medial temporal cortex participates in controlled functions of active semantic association or integration. This area may be particularly important for integrating semantic representations with the ongoing linguistic context or discourse or, more generally, with episodic memory traces. Thus the results of the efMRI and ERP experiments were highly complementary.

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