Left Inferior Prefrontal Cortex Activity Reflects Inhibitory Rather Than Facilitatory Priming

Eileen R. Cardillo[1], Jennifer Aydelott[2], Paul M. Matthews[1], and Joseph T. Devlin[1]

Abstract

■ Functional neuroimaging has demonstrated reduced activation correlated with behavioral priming effects, a finding generally interpreted in terms of facilitated retrieval of target items in the context of related primes. Without a neutral prime, however, one cannot separate facilitatory effects of related primes from inhibitory effects of unrelated primes. Here we report an auditory semantic priming paradigm with congruent ("The boy bounced the BALL"), neutral ("The next item is BALL"), and incongruent ("Pasta is my favorite kind of BALL") sentence trials. As previously reported, reduced left inferior prefrontal cortex activation was observed for congruent relative to incongruent trials; however, the neutral condition allowed us to show that the effect arose from increased activation in the incongruent condition rather than reduced activation for congruent trials. Our results suggest that the left inferior prefrontal cortex inhibits interference from prepotent representations in order to select a task-appropriate target, and is consistent with its broader role in behavioral inhibition. ■

INTRODUCTION

Recognizing spoken words is deceptively easy, but in fact many component processes are involved. The speech stream must be parsed into acoustic features and then mapped onto meanings; phonological, semantic, and syntactic ambiguities must be resolved; and the words must be integrated into an existing context—all of which happens in under a second. Models of spoken word recognition typically assume at least three stages of processing in the comprehension of words in context: the activation of possible word candidates on the basis of the acoustic input, the selection from among these candidates of the most appropriate word, and the integration of the selected word meaning into the overall meaning of the sentence (e.g., Marslen-Wilson, 1989). Studies using behavioral measures have shown that the meaningful context in which a word occurs plays a significant role in how efficiently the word is recognized. Words that are compatible with the overall meaning of a sentence are processed easily and rapidly, whereas words that are incompatible with the context are processed more slowly (Neely, 1991; Stanovich & West, 1983). Thus, semantic context has both a facilitatory and an inhibitory effect on spoken word comprehension.

At a behavioral level, priming paradigms are often used to differentiate between the facilitatory and inhibitory effects of meaningful context. For example, subjects are faster to decide that "doctor" is a word when it is preceded by a semantically associated prime such as "nurse" rather than a semantically neutral prime, such as pink noise (i.e., noise limited to the frequencies of human speech). In contrast, responses to "doctor" are slowed relative to a neutral context when preceded by a semantically unrelated prime (e.g., "table"). Thus, when unrelated and related pairs are directly compared (i.e., without reference to a neutral baseline), both facilitation and inhibition contribute to the observed effect on reaction times (Neely, 1991). Facilitation is associated with the activation of word meaning representations, and is generally considered to reflect the operation of automatic, fast acting processes, which occur without an individual's intention or awareness. In contrast, slower, strategically controlled mechanisms that do require a person's intention or conscious awareness can both facilitate and inhibit target recognition (Neely, 1991; Posner & Snyder, 1975). In this article, we investigated the neural correlates of facilitatory and inhibitory priming in comprehension of spoken words in a semantic context, with a specific focus on the left inferior prefrontal cortex (LIPC).

To date, only a handful of functional neuroimaging investigations of semantic priming in single words have been conducted, each finding reduced neural activity associated with primed than unprimed items, but with differences in localization of these priming effects (Rossell, Price, & Nobre, 2003; Kotz, Cappa, von Cramon, & Friederici, 2002; Rossell, Bullmore, Williams, & David, 2001; Mummery, Shallice, & Price, 1999). More com-

[1]University of Oxford, [2]University of London

monly, imaging studies have employed repetition priming tasks, repeatedly demonstrating reduced LIPC activity for primed items across a range of tasks and stimuli (van Turennout, Bielamowicz, & Martin, 2003; Wagner, Koutstaal, Maril, Schacter, & Buckner, 2000; Thompson-Schill, D'Esposito, & Kan, 1999; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997; Gabrieli et al., 1996; Demb et al., 1995). For example, Demb et al. (1995) used functional magnetic resonance imaging (fMRI) to measure brain activation while subjects made concrete/abstract judgments of written words. When a target item was repeated, subjects responded more quickly and there was a corresponding reduction of blood oxygen level dependent (BOLD) signal in LIPC. These repetition-based decreases cannot be explained solely by perceptual overlap as they also have been observed with cross-modal repetition (Buckner, Koutstaal, Schacter, & Rosen, 2000) and when the prime and the target were pictures of different objects sharing the same name, such as two types of chairs (Vuilleumier, Henson, Driver, & Dolan, 2002). Instead, these effects been interpreted as evidence that primes reduce the demands on amodal controlled processes such as lexical search and access, making the processing of repeated targets more efficient. Thus, although repetition priming and semantic priming differ behaviorally in several important ways, including the duration of effect, sensitivity to intervening items, and responsiveness to manipulations of attentional allocation (Wiggs & Martin, 1998; Neely, 1991; Farah, 1989), both types of priming lead to reduced neural activity, suggesting that priming facilitates retrieval.

Another possibility should be considered, however. The processing demands in the LIPC may also be *increased* by an unrelated prime in much the same way that an unrelated prime inhibits behavioral responses. The relative reduction in the LIPC signal for primed targets could thus arise from increased signal for unprimed targets rather than decreased signal for primed targets. This alternative interpretation is potentially important because it suggests that the LIPC is involved in the suppression of competing information rather than the automatic activation or controlled retrieval of representations.

One particularly robust method for distinguishing between behavioral facilitation and inhibition is the sentence priming paradigm. In this task, participants listen to sentences and make a response to the final word. Sentence completions are either semantically congruent ("The boy bounced the BALL"), neutral ("The next item is CHAIR"), or incongruent ("Pasta is my favorite kind of WALL"). Congruent sentences typically produce strong facilitation relative to neutral trials while incongruent trials elicit a smaller, inhibitory effect on response time (RT) (e.g., Stanovich & West, 1981, 1983). As with single-word semantic priming, the speeded responses in congruent trials

are believed to generally reflect rapid, relatively automatic facilitation, whereas the response delay underlying inhibition is presumed to reflect the operation of slower, attentionally mediated mechanisms (Aydelott & Bates, 2004; Moll, Cardillo, & Aydelott Utman, 2001).

In the present study, we used a sentence priming task with fMRI to investigate the neural correlates of facilitation and inhibition effects. Participants listened to blocks of forward and digitally reversed sentences. In the forward blocks, a female voice read a sentence fragment such as "There was no hair on his —". The final (or target) word was then spoken by a male voice and subjects indicated by a button press whether the target was a real English word (e.g., "head") or not (e.g., "narb"). Semantically congruent (CON), neutral (NEUT), and incongruent (INCON) trials were pseudorandomly presented within the forward sentence blocks. In order to distinguish the system engaged in sentence processing from that responsible for general acoustic processing, forward sentences were contrasted with digitally reversed sentences. These reversed sentences were unintelligible and lacked semantic and syntactic information but matched forward sentences in acoustic complexity. Within these regions, we then identified areas showing significant priming effects (CON < INCON) and evaluated the signal change associated with facilitatory and inhibitory priming. In brief, we expected facilitatory priming would speed reaction times and reduce BOLD signal relative to neutral trials, whereas inhibitory priming would increase both reaction times and BOLD signal.

RESULTS

Behavioral Data

RTs were recorded from the onset of the target and the median RT for correct responses per condition per subject was used in the statistical analyses to minimize the effect of outliers (Ulrich & Miller, 1994; Wilcox, 1992). As predicted, responses were faster for congruent than neutral trials (mean = 238 msec) and slower for incongruent than neutral trials (mean = 47 msec, see Table 1). A one-way analysis of variance (ANOVA) indicated a significant main effect of context (CON, NEUT, INCON) on reaction times [$F(2,22) = 43.3, p < .001$]. Planned comparisons confirmed that participants responded significantly faster to congruent than neutral trials [$t(11) = 7.0, p < .001$]. This facilitation was seen numerically in all 12 participants. Incongruent trials led to a mean 47 msec increase in RT relative to neutral trials [$t(11) = 1.4, p < .10$], with 7 out of 12 participants showing numerically slower responses (i.e., inhibition). A one-way ANOVA comparing percent accuracy across priming trials also indicated a main effect of context [$F(2,22) = 20.2, p < .001$]. In this case, the effect was driven by significantly higher accuracy in

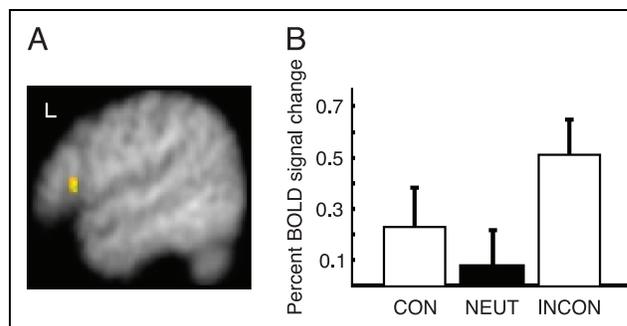**Table 1.** Mean Reaction Times (msec) and Accuracy to the Final Word in Each Sentence
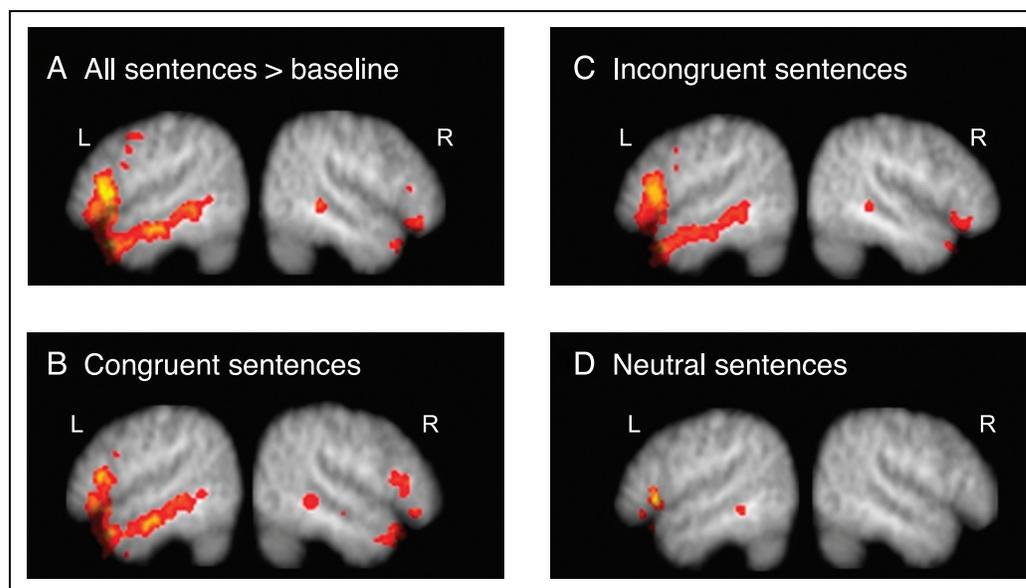
	Lexical Decisions			Gender Decision
	Congruent	Neutral	Incongruent	Reversed
Reaction time (standard error mean)	891 (31)	1129 (37)	1176 (27)	862 (48)
Accuracy (standard error mean)	99% (0.7)	89% (2.2)	87% (2.4)	99% (0.4)

Figure 2. Priming related activation reductions in the LIPC. (A) Activation is shown on a parasagittal slice of the group mean structural in standard space. (B) Effect sizes (mean % BOLD signal change) for each experimental condition in the activated region of the LIPC.

congruent relative to neutral contexts [$t(11) = 5.1, p < .001$]. These results confirm that congruent contexts are associated with strong facilitation and incongruent contexts are associated with weaker inhibition, consistent with previous studies (Stanovich & West, 1981, 1983).

Imaging Data

To identify regions engaged by sentence processing, all four types of forward sentences (CON, NEUT, INCON, and nonword trials) were contrasted with the digitally reversed stimuli baseline. This revealed significant activation in a network of regions in both hemispheres (Figure 1). In the left hemisphere, a single cluster extended from the inferior frontal gyrus onto the lateral temporal pole and along the extent of the entire middle temporal gyrus. Although less extensive, homologous activation regions were found in the right hemisphere. Additional areas of cortical activation included the left anterior fusiform gyrus, the precentral and medial frontal areas, and the left inferior parietal cortex (see Table 2). This pattern is consistent with other studies requiring auditory or visual processing of sentences (Vandenberghe, Nobre, & Price, 2002; Humphries, Willard, Buchsbaum, & Hickok, 2001; Dapretto & Bookheimer, 1999; Mazoyer et al., 1993) and, along with the behavioral data, indicates that participants were attending to the sentences. Similar patterns of activation were observed when congruent and incongruent trials were separately compared to baseline (Figure 1B and C). Neutral trials, on the other hand, produced less extensive activation (Figure 1D), possibly due to weaker semantic and syntactic integration demands for these simple, repeated sentence contexts.

Priming effects were identified within the brain regions showing a main effect of sentence processing.

Figure 1. Main effects of sentence processing relative to digitally reversed sentences. All activations are shown on two parasagittal slices of the group mean structural scan in standard space. (A) The main effect of sentence processing for all sentences relative to baseline. Simple main effects of each condition relative to baseline are shown for (B) congruent trials > baseline, (C) incongruent trials > baseline, and (D) neutral trials > baseline.

Table 2. Activations for all Forward Sentences Relative to Digitally Reserved Stimuli

| Description | Hemisphere | Peak Coordinate | | | Z-score |
		x	y	z	
Temporal					
Temporal pole	L	−52	18	−30	5.5
	R	54	14	−30	4.2
Anterior MTG	L	−56	−6	−16	5.5
Middle MTG	L	−60	−24	−10	5.2
	R	48	−36	−2	4.3
Posterior MTG	L	−58	−38	−6	5.3
Inferior temporal gyrus	L	−42	−48	−20	4.1
Anterior fusiform gyrus	L	−34	−4	−46	5.5
Frontal					
IFG (pars triangularis)	L	−50	24	8	5.5
	R	56	24	8	3.4
IFG (pars orbitalis)	L	−40	26	−10	5.3
	R	44	34	−16	4.6
Precentral gyrus	L	−56	4	36	4.6
	L	−44	−8	66	4.2
	R	42	−12	64	3.6
Frontal eye fields	L	−28	−12	68	3.5
	R	24	−12	68	3.5
Pre-SMA	L	−8	12	52	4.0
Superior frontal gyrus	R	8	32	46	3.7
Parietal lobes					
Inferior parietal	L	−26	−46	72	3.6
Other					
Basal ganglia	L	−20	2	6	3.6
Cerebellum	L	−48	−50	−30	5.0
Hippocampus	L	−34	−14	−20	3.8

Peak coordinates for each region are provided in standard space. L = left; R = right; IFG = inferior frontal gyrus; MTG = middle temporal gyrus; SMA = supplemental motor area.

Relative to incongruent trials, congruent trials produced a single highly significant reduction in BOLD signal in the pars opercularis region of the LIPC (−52, 20, 6; Z = 6.76; Figure 2A). Even when the statistical threshold was lowered to Z > 2.3 ($p < .01$, uncor-

rected), no other regions of reduced activity were identified. To determine whether this difference in the LIPC was correlated with facilitation, inhibition, or a combination of the two, we calculated a one-way repeated measures ANOVA with context (CON, NEUT, INCON) as a within-subjects factor and the mean percent BOLD signal change in the region of interest as the dependent measure. There was a significant main effect [$F(2,46) = 10.3$, $p < .001$] with planned comparisons indicating that this was due to an increase in BOLD signal for incongruent relative to neutral trials [$t(23) = −3.9$, $p < .001$] rather than a decrease for congruent trials (Figure 2B). There was no significant difference between congruent and neutral trials in the pars opercularis [$t(23) = 1.1$, *ns*]. Finally, there were no areas where congruent trials led to greater activation than incongruent trials, even at a more lenient Z-threshold of 2.3 ($p < .01$, uncorrected).

DISCUSSION

Like earlier functional neuroimaging investigations of repetition priming (van Turennout et al., 2003; Vuilleumier et al., 2002; Buckner et al., 2000; Wagner, Koutstaal, et al., 2000; Thompson-Schill, D'Esposito, & Kan, 1999; Wagner, Desmond, et al., 1997; Gabrieli et al., 1996; Demb et al., 1995), we found that a decrease in reaction times for primed items was associated with a reduction in BOLD signal in the LIPC, specifically in the pars opercularis. Previously, this result has been interpreted as indicating that a prime leads to more efficient retrieval of the target and thus less prefrontal activity. However, despite the strong behavioral facilitation (238 msec) seen in the current study, we found no imaging evidence to support this hypothesis, as LIPC responses were equivalent for congruent and neutral trials. Rather, the signal change was due to *increased* activity associated with incongruent sentence completions. In these trials, subjects responded to the unexpected, incongruent word presented rather than to the semantically plausible word primed by the context. Thus, they had to make a decision on the target in the face of strong competition from the primed representation, which had to be ignored or suppressed. This result suggests a different interpretation for the semantic priming effect found in our study from that of the repetition priming effects in previous fMRI studies: We propose that the pars opercularis region of the LIPC inhibits the interference from a prepotent representation to allow for the selection of task-appropriate information or representations. This hypothesis is consistent with previous suggestions that the LIPC plays a critical role in selecting among competing semantic alternatives (Thompson-Schill, D'Esposito, & Kan, 1999; Thompson-Schill, Swick, et al., 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), and may operate as part of a

larger semantic executive system (Wagner, Maril, Bjork, & Schacter, 2001).

The current findings depend on the neutral condition for distinguishing between the effects of facilitation and inhibition. It is possible, however, that the BOLD response to neutral trials was underestimated because primes and targets were modeled together. In other words, within the current analysis, BOLD responses reflected the combined processing of the sentence context and the target word. Although sentences were carefully matched in the congruent and incongruent conditions (see Methods), neutral primes were necessarily simpler and repeated. As a result, they presumably required less semantic and syntactic processing than either congruent or incongruent trials and may have led to a smaller BOLD signal. Indeed, the activation associated with the neutral trials suggests they were processed much like single words (Binder, 1997; Price et al., 1996; Demonet et al., 1992). Even so, it is clear from Figure 2B that the BOLD response in the LIPC was numerically, although not significantly, smaller for neutral than congruent trials. Thus, even if this response was underestimated, an increase of 200–300% would not change the pattern of results; incongruent trials would still evoke a significantly stronger response than congruent or neutral trials.

Although the current study focused specifically on semantic priming, the results may also be relevant to the interpretation of repetition priming findings. Behavioral studies have clearly demonstrated that both facilitation and inhibition contribute to repetition priming effects even in paradigms as diverse as word–stem completion, object/nonobject decisions, and picture naming (Ratcliff & McKoon, 1996). Although prior exposure to an identical stimulus facilitates subsequent responses, prior exposure to a perceptually similar, but not identical, stimulus inhibits responses. Because this factor has not been explicitly manipulated or controlled in previous imaging experiments of repetition priming, inhibition may also contribute to the observed "reduction" previously found in LIPC activity.

These results are also compatible with neuropsychological investigations demonstrating deficits in several aspects of executive function in language tasks for patients with LIPC lesions. For instance, such patients are impaired at suppressing a currently active representation in order to generate an appropriate response (Burgess & Shallice, 1996; Perret, 1974); they have deficits when retrieving information in a relatively unconstrained context (Robinson, Blair, & Cipolotti, 1998; Costello & Warrington, 1989); and they have greater difficulty selecting between competing semantic alternatives (Metzler, 2001; Thompson-Schill, Swick, et al., 1998). These findings all support the role of the LIPC in mediating competition between distracting, task-irrelevant representations and task-appropriate target representations.

Additional evidence comes from behavioral studies of patients with Broca's aphasia, which is also associated with lesions to the LIPC. Increased LIPC activity for incongruent trials is consistent with the finding that Broca's aphasics exhibit abnormal semantic priming effects (Blumstein & Milberg, 2000; Milberg, Blumstein, & Dworetzky, 1987, 1988). Further, Broca's patients are more vulnerable than normal individuals to competition from acoustically similar items (Aydelott Utman, Blumstein, & Sullivan, 2001), are impaired in their selection of the appropriate meaning of ambiguous words (Swaab, Brown, & Hagoort, 1998), and have difficulty recovering from violations of stimulus-generated expectancies (Milberg, Blumstein, Katz, & Gershberg, 1995; Milberg, Blumstein, & Dworetzky, 1987). These findings provide further support for the claim that the LIPC is involved in the selection of an appropriate lexical item from a set of alternatives. However, Blumstein and Milberg (2000) argue that Broca's aphasics suffer from a reduction in lexical activation, rather than an inhibitory-selection deficit, based on the overall pattern of performance of these patients across a variety of tasks (but cf. Hagoort, 1997; Ostrin & Tyler, 1993). It is worth noting that the reduced activation hypothesis is based on evidence from a different experimental paradigm than that reported here: word–word priming, as opposed to sentence priming. Priming effects in word–word paradigms are generally thought to reflect mechanisms operating within the mental lexicon, including the activation of lexical representations on the basis of sensory input, spreading activation within the lexical network, and lateral inhibition and/or competition between lexical items (Aydelott Utman et al., 2001; Neely, 1991; Meyer & Schvaneveldt, 1976), in addition to postlexical processes (Neely, 1991). The sentence priming task reported here may more closely reflect semantic integration processes and the generation of expectancies, particularly as our paradigm used highly constraining sentence contexts (as discussed in further detail below).

It is also important to distinguish between the clinical syndrome of Broca's aphasia and damage to the LIPC and/or Broca's area. A diagnosis of Broca's aphasia does not reliably predict a lesion in Broca's area, nor does an anterior/Broca's area lesion necessarily result in Broca's aphasia (e.g., Wilmes & Poeck, 1993; Dronkers, Shapiro, Redfern, & Knight, 1992). The precise nature of the language deficits observed in Broca's aphasia and the underlying neural structures associated with this syndrome are still being explored. Thus, the possibility remains that Broca's aphasics suffer from an impairment at the lexical level involving the activation of lexical items from sensory information (Aydelott Utman et al., 2001; Milberg, Blumstein, & Dworetzky, 1988), which may contribute to difficulties in the selection and maintenance of lexical representations. Nevertheless, the present results clearly demonstrate that the LIPC is involved in the recovery from violations of semantic constraint,

suggesting that this region plays a role in the inhibition of irrelevant information in higher-level language processing. Whether this accounts for other aspects of language processing in Broca's aphasia remains a topic for future research.

Mechanisms of Priming

Semantic priming is hypothesized to arise from three types of processes: automatic activation, controlled integrative processes, and controlled expectancy mechanisms. Automatic activation occurs when target words are pre-activated by related words in the preceding context, either as a result of associative links or shared semantic features. This process facilitates the retrieval of and response to related targets but does not have any inhibitory effect on unrelated targets (Meyer & Schvaneveldt, 1976). In contrast, integration and expectancy mechanisms can contribute to both facilitation and inhibition. Integration occurs as semantic and syntactic information builds into a single conceptual representation of the unfolding sentence (Traxler & Foss, 2000; Connolly & Phillips, 1994; Holcomb, 1993). Because semantically incongruent completions are difficult to integrate into the preceding context, they slow responses; whereas semantically congruent completions are easily and rapidly incorporated into the overall meaning of the sentence. Additionally, an expectancy mechanism generates a set of predictable words based on the current context (i.e., the prime), thereby facilitating the recognition of these anticipated words. When an unexpected target occurs, however, response is delayed as attention shifts from the expected item(s) to the presented item (Neely, 1991). The sentence priming paradigm used here most likely engages all three mechanisms, but may primarily reflect expectancies due to the highly constrained contexts presented.

Importantly, the only previous fMRI study of semantic priming to report reduced activation in the LIPC for related pairs relative to unrelated pairs also used stimuli likely to induce expectancies. Kotz et al. (2002) included associated word pairs such as BREAD–BUTTER in a word–word priming paradigm and found that related relative to unrelated pairs activated the LIPC at −47, 22, 14. Given that word associations measure the likelihood of two words occurring together, in their study it was possible to predict a target from its prime in much the same way that a congruent sentence makes a target predictable. In contrast to associated word pairs, categorically related pairs (e.g., TABLE–SOFA) consist of primes semantically related to, but not predictable from, their targets. Accordingly, studies using such categorically related pairs have not found priming effects in the LIPC (Rossell, Price, et al., 2003; Rossell, Bullmore, et al., 2001; Mummery et al., 1999). Taken together, these findings suggest that the greater activation in the LIPC for incongruent sentences (current study) and unrelated primes (Kotz et al., 2002) may reflect expectancy violations.

Semantic integration also plays an important role in sentence priming, and has been extensively studied with event-related potentials (ERPs). These studies consistently find that incongruent trials elicit a negative component peaking approximately 400 msec after the anomalous word, the so-called N400 signature (Kutas & Hillyard, 1984). The N400 component is attenuated by a congruent semantic context and increased by an incongruent semantic context. A similar N400 effect is observed in sentence–word and word–word paradigms (Van Petten, 1995), and in both cases is considered to reflect the difficulty of integrating a target into a preceding context (Holcomb, 1993; Rugg, 1990). In vivo subdural grid recordings in presurgical epilepsy patients have demonstrated an N400 source near the anterior collateral sulcus on the ventral surface of the anterior temporal poles (McCarthy, Nobre, Bentin, & Spencer, 1995; Nobre & McCarthy, 1995). Although the behavioral results of the current study are consistent with those in previous ERP studies, we did not observe any difference in activation between incongruent and congruent sentence completions in this ventral temporal region, even after lowering the statistical threshold to $Z > 2.3$ ($p < .01$, uncorrected). This may be at least partly due to differences in the temporal sensitivity of fMRI and ERP, as ERPs are equally sensitive to early and late potentials while BOLD signal largely reflects later, summed potentials (Lauritzen, 2001). Nonetheless, the lack of activity corresponding to an N400 potential suggests that semantic integration played a smaller role in the current paradigm than expectancy, which generated a robust LIPC signal.

In contrast, several previous functional neuroimaging studies of semantic priming have reported priming effects in the anterior ventral temporal area, presumably due to semantic integration (Rossell, Price, et al., 2003; Rossell, Bullmore, et al., 2001; Mummery et al., 1999). These studies used word–word priming where primes and targets were members of the same category (e.g., PIG–HORSE). This paradigm emphasizes "pure" semantic relations between the prime and target (Moss, Ostrin, Tyler, & Marslen-Wilson, 1995) and thus, the temporal lobe priming effect likely reflects facilitated integration as a result of shared semantic features between prime and target, an interpretation consistent with recent ERP work (Federmeier & Kutas, 1999).

Although we have focused on the linguistic role of the LIPC, it is clear that these processes are not specific to language. Discrimination reversal and go/no-go tasks engage the LIPC and its right hemisphere homologue (collectively referred to as the ventrolateral prefrontal cortex, or VLPFC) in both humans (Durston, Thomas, Worden, Yang, & Casey, 2002) and other primates (Dias, Robbins, & Roberts, 1996; Iversen & Mishkin, 1970). Bunge, Ochsner, Desmond, Glover, and Gabrieli

(2001) have suggested inhibitory processes are actually a subset of working memory processes controlled by the prefrontal cortex, with the VLPFC having a greater role in filtering out irrelevant information and selecting among competing stimuli, responses, memories, or associations (see also Barde & Thompson-Schill, 2002). Likewise, Levy and Anderson (2002) suggest common inhibitory mechanisms in the prefrontal region underlie response-override tasks in the perceptual–motor and memory domains. The current study suggests these same processes also play an important role in language processing.

METHODS

Participants

Twelve right-handed, native British English speakers (3 women, 9 men) between 18 and 34 years of age (mean = 22) participated in the experiment after giving written informed consent. None reported hearing impairments or any history of neurological disease. The study was approved by the Central Oxford Research Ethics Committee.

Procedure

There were two experimental tasks. In the first, participants heard auditory sentences spoken by a female voice immediately followed by a target word spoken in a male voice. Participants made a lexical decision to the target as quickly and accurately as possible by pressing the left response key if they heard a real English word or the right key if they heard a nonword. The next trial began 1500 msec after their response. In the second task, digitally reversed sentences were presented and participants were instructed to press the left key as soon as they detected the switch in the gender of the speaker. Reversed trials matched the normal speech stimuli in terms of acoustic complexity but lacked semantic content, thus serving as a low-level baseline for identifying the neural regions engaged by sentence processing.

The priming stimuli consisted of 120 semantically biased sentence contexts (60 ending with words and 60 ending with nonwords) and a single semantically neutral context. Biased contexts were approximately 10 syllables in length (mean = 10.0, $SD = 2.7$) and 2 sec in duration (mean = 2.0, $SD = 0.48$). Sixty monosyllabic words containing three to five phonemes (mean = 3.3, $SD = 0.65$) and a mean duration of 0.78 sec ($SD = 0.12$) served as their completions. These targets had a mean print frequency of 139 ($SD = 99$) (Kucera & Francis, 1967), a mean spoken frequency of 14 ($SD = 81$)(Brown, 1984), and a mean concreteness rating of 546 ($SD = 81$) (Coltheart, 1981). Targets assigned to each of the priming conditions did not differ significantly from each other along any of these dimensions. Further, to avoid possible

morphological and morpho-phonological constraints of determiners (a/an, the), mass nouns such as "blood" and "dust" were excluded, and all targets were consonant–initial. The nonword distracter targets consisted of phonologically permissible one-syllable nonsense items, which did not differ significantly from the targets in terms of number of phonemes or duration. A subset of these contexts and targets ($n = 60$) was digitally reversed and used as stimuli in the baseline condition.

Because each sentence prime occurred only in a single condition (i.e., they were not repeated), context and target stimuli in each priming condition were carefully matched along a number of dimensions. Foremost, there was no significant difference in length, duration, number of words related to the target, or number of content words between sentences paired with congruent targets and those paired with incongruent targets, nor between sentences paired with word targets and those paired with nonwords. Pilot analyses showed that 98% ($SD = 0.04$) of all subjects (none of whom participated in the current experiment) completed contexts assigned to the congruent condition with the same word, just as 97% ($SD = 0.04$) of subjects finished the contexts assigned to the incongruent condition with the same word. Thus, sentence contexts assigned to the congruent condition and those assigned to the incongruent condition did not differ significantly in contextual constraint, or in the degree to which they semantically biased a particular completion. In contrast, congruent and incongruent contexts did differ significantly in terms of the cloze probability of their assigned targets, or the likelihood that their target words were given as suitable completions in the pilot test. Targets matched with the semantically congruent sentence contexts were the most frequently given completions, thus having a mean cloze probability of 0.98 ($SD = 0.04$). Targets matched with semantically incongruent contexts, however, were never given as possible completions in the pilot test, thereby rendering their cloze probability 0. "The next item is —" was selected as the neutral baseline on the basis of its precedent in psycholinguistic and ERP studies of sentence priming, and evidence that use of several different neutral contexts may underestimate the already small inhibition effects (Aydelott & Bates, 2004; Taft, 1991; Stanovich & West, 1983). Behavioral pretesting with a separate group of 10 participants confirmed the effectiveness of the contexts as semantic primes. As expected, congruent contexts resulted in significantly faster lexical decisions than the neutral context [mean = 197 msec, $t(9) = 10.0$, $p < .001$], and incongruent contexts resulted in significantly slower responses [mean = 54 msec, $t(9) = 3.5$, $p < .01$].

During scanning, stimuli were presented to both ears through MRI compatible electrostatic headphones (Sennheiser HE 60) with modified industrial ear protectors (Bilsom 2452) at 90 dB SPL using SuperLab 2.0 software

(Cedrus, San Pedro, CA) and the Institute of Hearing Research sound system (Palmer, Bullock, & Chambers, 1998). Subjects received two sets of practice trials before beginning the experiment: The first was presented in silence to familiarize the subjects with the task, and the second was presented during echo-planar image (EPI) acquisition to familiarize them with hearing the stimuli despite the background scanner noise. Previous work has shown that priming effects are robust even in noisy conditions as long as the source of interference is spatially isolable from the target stimuli (Moll et al., 2001). In addition, unpublished data from our laboratory indicate that white noise masking in sentence–word priming does not affect the magnitude of priming effects at signal-to-noise ratios (SNR) of 1. Because the EPI-related sounds were spatially distinct from the experimental stimuli and the measured SNR of the auditory stimuli during scanning was +10, we anticipated adequate performance once participants were familiarized with the tasks and comfortable with the practice trials.

All subjects participated in two consecutive runs of scanning, counterbalanced across subjects. Each run began with 12 sec in which no sentences were presented to allow for T1 magnetic equilibrium and these scans were discarded before analysis. Scanning was carried out using the Varian-Siemens 3T scanner at the Centre for Functional Magnetic Resonance Imaging of the Brain in Oxford. A Magnex head-dedicated gradient insert coil was used in conjunction with a birdcage head radio-frequency coil tuned to 127.4 MHz. Functional imaging consisted of 21 T2*-weighted EPI slices (TE = 30 msec, FOV = 192 by 256 mm, matrix = 64 by 64) giving a notional $3 \times 4 \times 5$ mm resolution. An automated shimming algorithm was used to reduce magnetic field inhomogeneities (Wilson et al., 2002). In addition, a T1-weighted scan was acquired (3D Turbo FLASH sequence, TR = 15 msec, TE = 6.9 msec) with 1 mm^2 in-plane resolution and 1.5 mm slice thickness for the purpose of anatomical localization.

Analyses

Functional images were realigned (Jenkinson, Bannister, Brady, & Smith, 2002) using the FSL software (www. fmrib.ox.ac.uk/fsl) in order to correct for small head movements. No participant moved more than 1.5 mm in any direction and rotations were less than 1.5°. Functional images were registered to the participant's structural scan and then to the MNI 152-mean brain using an affine procedure (Jenkinson & Smith, 2001). Finally, each image was smoothed with a 5-mm full width half maximum gaussian filter. The FSL software was used to compute individual subject analyses using the general linear model after pre-whitening (Woolrich, Ripley, Brady, & Smith, 2001) with congruent, neutral, incongruent, nonword, and reversed trials modeled separately. In addition, temporal derivatives and estimated motion parameters were included as covariates of no interest to increase statistical sensitivity. Random effects group analyses identified significantly activated brain regions. A cluster-based significance test (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994) was used to identify the main effects of each sentence-type relative to reversed sentences. Voxels were thresholded at $Z > 3.1$ and clusters were considered significant only if their spatial extent was larger than that of a corresponding null hypothesis at $p < .05$, corrected for multiple comparisons. A conjunction analysis (Worsley & Friston, 2000; Price & Friston, 1997) was used to limit the priming comparisons (CON vs. INCON) to regions showing a main effect of sentence processing.

REFERENCES

Aydelott, J., & Bates, E. (2004). Effects of acoustic distortion and semantic context on lexical access. *Language and Cognitive Processes, 19*, 29–56.

Aydelott Utman, J., Blumstein, S. E., & Sullivan, K. (2001). Mapping from sound to meaning: Reduced lexical activation in Broca's aphasics. *Brain and Language, 79*, 444–472.

Barde, L. H., & Thompson-Schill, S. L. (2002). Models of functional organization of the lateral prefrontal cortex in verbal working memory: Evidence in favor of the process model. *Journal of Cognitive Neuroscience, 14*, 1054–1063.

Binder, J. R. (1997). Neuroanatomy of language processing studied with functional MRI. *Clinical Neuroscience, 4*, 87–94.

Blumstein, S. E., & Milberg, W. P. (2000). Language deficits in Broca's and Wernicke's aphasia: A singular impairment. In Y. Grodzinsky & L. P. Shapiro (Eds.), *Language and the brain: Representation and processing* (pp. 167–183). San Diego, CA: Academic Press.

Brown, G. D. A. (1984). A frequency count of 190,000 words in the London-Lund Corpus of English Conversation. *Behavioural Research Methods, Instrumentation and Computers, 16*, 502–532.

Buckner, R. L., Koutstaal, W., Schacter, D. L., & Rosen, B. R. (2000). Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. *Brain, 123*, 620–640.

Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., &

Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain, 124,* 2074–2086.

Burgess, P. W., & Shallice, T. (1996). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia, 34,* 263–272.

Coltheart, M. (1981). The MRC Psycholinguistics database. *Quarterly Journal of Experimental Psychology, 33A,* 497–505.

Connolly, J. F., & Phillips, N. A. (1994). Event-related potential components reflect phonological and semantic processing of the terminal word of spoken sentences. *Journal of Cognitive Neuroscience, 6,* 256–266.

Costello, A. L., & Warrington, E. K. (1989). Dynamic aphasia. The selective impairment of verbal planning. *Cortex, 25,* 103–114.

Dapretto, M., & Bookheimer, S. Y. (1999). Form and content: Dissociating syntax and semantics in sentence comprehension. *Neuron, 24,* 427–432.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience, 15,* 5870–5878.

Demonet, J.-F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J.-L., Wise, R., Rascol, A., & Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain, 115,* 1753–1768.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature, 380,* 69–72.

Dronkers, N. F., Shapiro, J. K., Redfern, B., & Knight, R. T. (1992). The role of Broca's area in Broca's aphasia. *Journal of Clinical and Experimental Neuropsychology, 14,* 52–53.

Durston, S., Thomas, K. M., Worden, M. S., Yang, Y., & Casey, B. J. (2002). The effect of preceding context on inhibition: An event-related fMRI study. *Neuroimage, 16,* 449–453.

Farah, M. J. (1989). Semantic and perceptual priming: How similar are the underlying mechanisms? *Journal of Experimental Psychology: Human Perception and Performance, 15,* 188–194.

Federmeier, K. D., & Kutas, M. (1999). A rose by any other name: Long-term memory structure and sentence processing. *Journal of Memory and Language, 41,* 469–495.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping, 1,* 214–220.

Gabrieli, J. D., Desmond, J. E., Demb, J. B., Wagner, A. D., Stone, M. V., Vaidya, C. J., & Glover, G. H. (1996). Functional magnetic resonance imaging of semantic memory processes. *Psychological Science, 7,* 278–283.

Hagoort, P. (1997). Semantic priming in Broca's aphasics at a short SOA: No support for an automatic access deficit. *Brain and Language, 56,* 287–300.

Holcomb, P. J. (1993). Semantic priming and stimulus degradation: Implications for the role of the N400 in language processing. *Psychophysiology, 30,* 47–61.

Humphries, C., Willard, K., Buchsbaum, B., & Hickok, G. (2001). Role of anterior temporal cortex in auditory sentence comprehension: An fMRI study. *NeuroReport, 12,* 1749–1752.

Iversen, S. D., & Mishkin, M. (1970). Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research, 11,* 376–386.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17,* 825–841.

Jenkinson, M., & Smith, S. M. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5,* 143–156.

Kotz, S. A., Cappa, S. F., von Cramon, D. Y., & Friederici, A. D. (2002). Modulation of the lexical–semantic network by auditory semantic priming: An event-related functional MRI study. *Neuroimage, 17,* 1761–1772.

Kucera, H., & Francis, W. M. (1967). *Computational analysis of present-day American English.* Providence, RI: Brown University Press.

Kutas, M., & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature, 307,* 161–163.

Lauritzen, M. (2001). Relationship of spikes, synaptic activity, and local changes of cerebral blood flow. *Journal of Cerebral Blood Flow and Metabolism, 21,* 1367–1383.

Levy, B. J., & Anderson, M. C. (2002). Inhibitory processes and the control of memory retrieval. *Trends in Cognitive Sciences, 6,* 299–305.

Marslen-Wilson, W. (1989). Access and integration: Projecting sound onto meaning. In W. Marslen-Wilson (Ed.), *Lexical representation and process* (pp. 3–24). Cambridge: MIT Press.

Mazoyer, B. M., Tzourio, N., Frak, V., Syrota, A., Murayama, N., & Levrier, D. (1993). The cortical representation of speech. *Journal of Cognitive Neuroscience, 5,* 467–479.

McCarthy, G., Nobre, A. C., Bentin, S., & Spencer, D. D. (1995). Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. *Journal of Neuroscience, 15,* 1080–1089.

Metzler, C. (2001). Effects of left frontal lesions on the selection of context-appropriate meanings. *Neuropsychology, 15,* 315–328.

Meyer, D. E., & Schvaneveldt, R. W. (1976). Meaning, memory structure, and mental processes. *Science, 192,* 27–33.

Milberg, W., Blumstein, S. E., & Dworetzky, B. (1987). Processing of lexical ambiguities in aphasia. *Brain and Language, 31,* 138–150.

Milberg, W., Blumstein, S., & Dworetzky, B. (1988). Phonological processing and lexical access in aphasia. *Brain and Language, 34,* 279–293.

Milberg, W., Blumstein, S. E., Katz, D., & Gershberg, F. (1995). Semantic facilitation in aphasia: Effects of time and expectancy. *Journal of Cognitive Neuroscience, 7,* 33–50.

Moll, K., Cardillo, E., & Aydelott Utman, J. (2001). Effects of competing speech on sentence–word priming: Semantic, perceptual, and attentional factors. *Proceedings of the Twenty-third Annual Conference of the Cognitive Science Society* (pp. 679–684). Mahwah, NJ: Erlbaum.

Moss, H. E., Ostrin, R. K., Tyler, L. K., & Marslen-Wilson, W. D. (1995). Accessing different types of lexical semantic information: Evidence from priming. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21,* 863–883.

Mummery, C. J., Shallice, T., & Price, C. J. (1999). Dual-process model in semantic priming: A functional imaging perspective. *Neuroimage, 9,* 516–525.

Neely, J. (1991). Semantic priming in visual word recognition: A selective review of the current theories and findings. In B. Besner & G. Humphries (Eds.), *Basic processes in reading: Visual word recognition.* Hillsdale, NJ: Erlbaum.

Nobre, A. C., & McCarthy, G. (1995). Language-related field potentials in the anterior-medial temporal lobe: II. Effects of

word type and semantic priming. *Journal of Neuroscience, 15,* 1090–1098.

Ostrin, R. K., & Tyler, L. K. (1993). Automatic access to lexical semantics in aphasia: Evidence from semantic and associative priming. *Brain and Language, 45,* 147–159.

Palmer, A. R., Bullock, D. C., & Chambers, J. D. (1998). A high-output, high quality sound system for use in auditory fMRI. *Neuroimage, 7,* S359.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia, 12,* 323–330.

Posner, M. I., & Snyder, C. R. R. (1975). Attention and cognitive control. In R. L. Solso (Ed.), *Information processing and cognition: The Loyola symposium.* Hillsdale, NJ: Erlbaum.

Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: A new approach to brain activation experiments. *Neuroimage, 5,* 261–270.

Price, C. J., Wise, R. J. S., Warburton, E. A., Moore, C. J., Howard, D., Patterson, K., Frackowiak, R. S. J., & Friston, K. J. (1996). Hearing and saying—The functional neuro-anatomy of auditory word processing. *Brain, 119,* 919–931.

Ratcliff, R., & McKoon, G. (1996). Bias effects in implicit memory tasks. *Journal of Experimental Psychology: General, 125,* 403–421.

Robinson, G., Blair, J., & Cipolotti, L. (1998). Dynamic aphasia: An inability to select between competing verbal responses? *Brain, 121,* 77–89.

Rossell, S. L., Bullmore, E. T., Williams, S. C., & David, A. S. (2001). Brain activation during automatic and controlled processing of semantic relations: A priming experiment using lexical-decision. *Neuropsychologia, 39,* 1167–1176.

Rossell, S. L., Price, C. J., & Nobre, A. C. (2003). The anatomy and time course of semantic priming investigated by fMRI and ERPs. *Neuropsychologia, 41,* 550–564.

Rugg, M. D. (1990). Event-related brain potentials dissociate repetition effects of high- and low-frequency words. *Memory and Cognition, 18,* 367–379.

Stanovich, K.-E., & West, R.-F. (1981). The effect of sentence context on ongoing word recognition: Tests of a two-process theory. *Journal of Experimental Psychology: Human Perception and Performance, 7,* 658–672.

Stanovich, K. E., & West, R. F. (1983). On priming by a sentence context. *Journal of Experimental Psychology: General, 112,* 1–36.

Swaab, T. Y., Brown, C., & Hagoort, P. (1998). Understanding ambiguous words in sentence contexts: Electrophysiological evidence for delayed contextual selection in Broca's aphasia. *Neuropsychologia, 36,* 737–761.

Taft, M. (1991). *Reading and the mental lexicon.* Hillsdale, NJ: Erlbaum.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences, U.S.A., 94,* 14792–14797.

Thompson-Schill, S. L., D'Esposito, M., & Kan, I. P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron, 23,* 513–522.

Thompson-Schill, S. L., Swick, D., Farah, M. J., D'Esposito, M., Kan, I. P., & Knight, R. T. (1998). Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proceedings of the National Academy of Sciences, U.S.A., 95,* 15855–15860.

Traxler, M. J., & Foss, D. J. (2000). Effects of sentence constraint on priming in natural language comprehension. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26,* 1266–1282.

Ulrich, R., & Miller, J. (1994). Effects of truncation on reaction time analyses. *Journal of Experimental Psychology: General, 123,* 34–80.

Van Petten, C. (1995). Words and sentences: Event-related brain potential measures. *Psychophysiology, 32,* 511–525.

van Turennout, M., Bielamowicz, L., & Martin, A. (2003). Modulation of neural activity during object naming: Effects of time and practice. *Cerebral Cortex, 13,* 381–391.

Vandenberghe, R., Nobre, A. C., & Price, C. J. (2002). The response of left temporal cortex to sentences. *Journal of Cognitive Neuroscience, 14,* 550–560.

Vuilleumier, P., Henson, R. N., Driver, J., & Dolan, R. J. (2002). Multiple levels of visual object constancy revealed by event related fMRI of repetition priming. *Nature Neuroscience, 5,* 491–499.

Wagner, A. D., Desmond, J. E., Demb, J. B., Glover, G. H., & Gabrieli, J. D. E. (1997). Semantic repetition priming for verbal and pictorial knowledge: A functional MRI study of the left inferior prefrontal cortex. *Journal of Cognitive Neuroscience, 9,* 714–726.

Wagner, A. D., Koutstaal, W., Maril, A., Schacter, D. L., & Buckner, R. L. (2000). Task-specific repetition priming in left inferior prefrontal cortex. *Cerebral Cortex, 10,* 1176–1184.

Wagner, A. D., Maril, A., Bjork, R. A., & Schacter, D. L. (2001). Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral Prefrontal cortex. *Neuroimage, 14,* 1337–1347.

Wiggs, C. L., & Martin, A. (1998). Properties and mechanisms of perceptual priming. *Current Opinion in Neurobiology, 8,* 227–233.

Wilcox, R. R. (1992). Comparing the medians of dependent groups. *British Journal of Mathematical and Statistical Psychology, 45,* 151–162.

Wilmes, K., & Poeck, K. (1993). To what extent can aphasic syndromes be localised? *Brain, 116,* 1527–1540.

Wilson, J. L., Jenkinson, M., de Araujo, I., Kringelbach, M. L., Rolls, E. T., & Jezzard, P. (2002). Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. *Neuroimage, 17,* 967–976.

Woolrich, M. W., Ripley, B. D., Brady, J. M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modelling of fMRI data. *Neuroimage, 14,* 1370–1386.

Worsley, K. J., & Friston, K. J. (2000). A test for conjunction. *Statistics and Probability Letters, 47,* 135–140.