Neuroimaging Studies of Word and Pseudoword Reading: Consistencies, Inconsistencies, and Limitations

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Abstract

■ Several functional neuroimaging studies have compared words and pseudowords to test different cognitive models of reading. There are difficulties with this approach, however, because cognitive models do not make clear-cut predictions at the neural level. Therefore, results can only be interpreted on the basis of prior knowledge of cognitive anatomy. Furthermore, studies comparing words and pseudowords have produced inconsistent results. The inconsistencies could reflect false-positive results due to the low statistical thresholds applied or confounds from nonlexical aspects of the stimuli. Alternatively, they may reflect true effects that are inconsistent across subjects; dependent on experimental parameters such as stimulus rate or duration; or not replicated across studies because of insufficient statistical power.

In this fMRI study, we investigate consistent and inconsistent differences between word and pseudoword reading in 20 subjects, and distinguish between effects associated with increases and decreases in activity relative to fixation. In addition, the interaction of word type with stimulus duration is explored. We find that words and pseudowords activate the same set of regions relative to fixation, and within this system, there is greater activation for pseudowords than words in the left frontal operculum, left posterior inferior temporal gyrus, and the right cerebellum. The only effects of words relative to pseudowords consistent over subjects are due to decreases in activity for pseudowords relative to fixation; and there are no significant interactions between word type and stimulus duration. Finally, we observe inconsistent but highly significant effects of word type at the individual subject level.

These results (i) illustrate that pseudowords place increased demands on areas that have previously been linked to lexical retrieval, and (ii) highlight the importance of including one or more baselines to qualify word type effects. Furthermore, (iii) they suggest that inconsistencies observed in the previous literature may result from effects arising from a small number of subjects only. ■

INTRODUCTION

This article is concerned with why functional neuroimaging studies investigating the differential effect of reading words and pseudowords on neuronal activation have produced such inconsistent results. By pseudowords, we refer to letter strings that are not real words, do not have semantic representations but can be pronounced on the basis of sublexical spelling to sound relationships (e.g., lenner). Below we briefly describe the cognitive models of reading that have motivated the functional neuroimaging studies. Then we discuss the ambiguous results from functional imaging studies and suggest hypotheses to explain the consistencies and inconsistencies in the literature. Finally, we present data from a new functional magnetic resonance imaging (fMRI) experiment that investigates the effect of word type and its interaction with stimulus duration.

Reports in the neuropsychological literature have shown that reading pseudowords can either be selectively impaired (phonological dyslexia) or relatively preserved (surface dyslexia). This observation led to theories that there might be separate neural processes involved in lexical and sublexical reading (e.g., see Marshall & Newcombe, 1973). Although both lexical and sublexical processes may be engaged irrespective of the type of letter string, successful pseudoword reading is reliant on sublexical processes, whereas familiar regularly spelled words can be read both lexically and sublexically. The alternative perspective, developed on the basis of computational modeling (Seidenberg & McClelland, 1989; McClelland & Rumelhart, 1981), makes no distinction between lexical and sublexical processes. Rather, the effect of word type results from changes in the connection strength between orthography, phonology, and semantics, with more semantic mediation for words than pseudowords. Figure 1 illustrates the dual route and connectionist models.

Although a number of functional neuroimaging studies have attempted to test alternative models of reading (Fiez & Petersen, 1998; Fiez, Balota, Raichle, & Petersen, 1999; Herbster, Mintun, Nebes, & Becker, 1997; Rumsey et al., 1997), these models do not make clear-cut predictions at the neural level. For example, a double dissociation in the activation patterns for reading words and pseudowords could either reflect (a) differential

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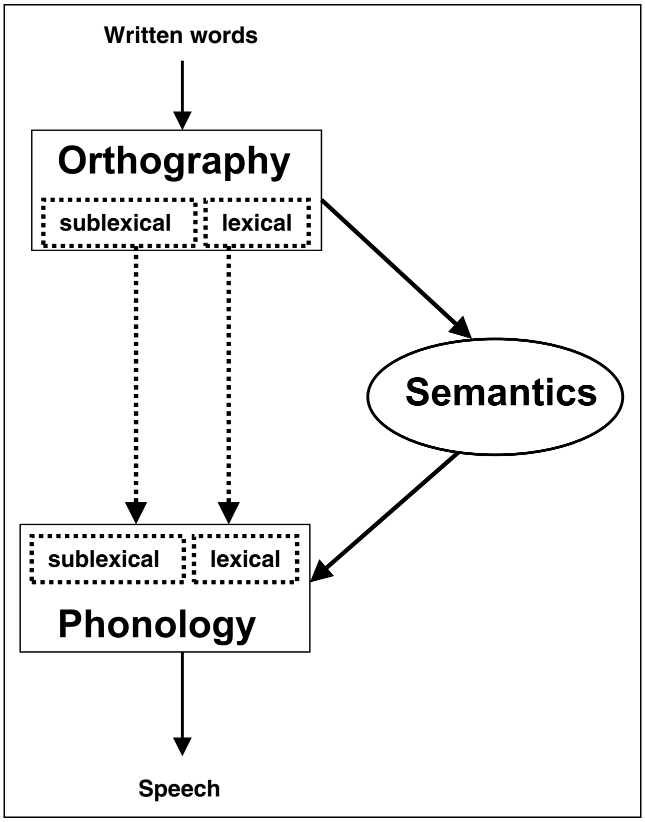

Figure 1. Dual route and connectionist models of reading. Solid lines pertain to both models, whereas dotted lines distinguish between distinct routes in the dual route model but not in the connectionist model. The dual route model places greatest emphasis on the distinction between the lexical and sublexical direct mappings from orthography to phonology. In addition, a third indirect route is also available via semantics. In contrast, the connectionist model does not distinguish between lexical and sublexical routes. Here the emphasis is on the connection strengths between orthography, phonology, and semantics. Both models postulate that phonological retrieval during reading can either occur via direct links between orthography and phonology or via indirect links that map orthography to semantics and semantics to phonology.

demands on lexical and sublexical routes, or (b) the degree to which semantics and phonology is activated for words and pseudowords, respectively (see Figure 1). Interpretation is therefore reliant on a prior understanding of which brain areas are involved in semantic, phonological, lexical, and sublexical word processing. Furthermore, the current neuroimaging literature has not revealed consistent differences between word and pseudoword reading (see Table 1 for summary).

The most consistent finding is that reading pseudowords relative to words increases activity in a number of language processing areas including the left inferior frontal gyrus (Xu et al., 2001; Paulesu et al., 2000; Brunswick, McCrory, Price, Frith, & Frith, 1999; Fiez et al., 1999; Hagoort et al., 1999; Herbster et al., 1997) and the inferior temporal gyrus (Xu et al., 2001; Paulesu et al., 2000; Brunswick et al., 1999; Price, Wise, & Frackowiak, 1996), but there have been no replications across studies when reading words is contrasted to reading pseudowords. Inconsistencies may be due to confounds from nonlexical aspects of the stimuli (e.g., differences in bigram frequency, visual input, or number of syllables) or they could reflect false-positive results due to the low statistical thresholds applied, which were not corrected for the number of comparisons being made. Alternatively, they may reflect (i) true effects that are inconsistent across subjects (different subjects may use different reading strategies); (ii) subtle effects which are not replicated across studies because of insufficient statistical power; or (iii) effects dependent on experimental parameters such as stimulus rate or duration (e.g., greater word type effects for longer stimulus durations). We conclude that further investigation is required to investigate consistent and inconsistent differences between word and pseudoword reading at a neural level.

In the present study, we used fMRI to investigate differences between word and pseudoword reading in 20 subjects. Subjects were instructed to read the words or pseudowords silently as soon as they appeared on the screen. Stimuli were presented in blocks of words or pseudowords alternated with fixation to a cross in the middle of the screen. Data were acquired in two different experiments. In the first experiment, stimulus duration was constant (600 msec) and stimulus rate varied (20, 40, or 60 words per minute). In the second experiment, stimulus rate was held constant (40 words per minute) and stimulus duration was manipulated (200, 600, and 1000 msec). Our aim was to identify (i) differences between word and pseudoword reading at a neural level; (ii) whether these differences reflect activation or deactivation relative to a neutral baseline (fixation); and (iii) whether a significant interaction between word type and stimulus duration can account for some of the inconsistencies in the neuroimaging literature.

In contrast with previous studies of word and pseudoword reading, the data were analyzed in a random-effect fashion, which allowed us to draw inferences pertaining to the population from which subjects came as opposed to the particular subjects studied (Friston, Holmes, & Worsley, 1999). When significant effects were not detected, we adopted a single-subject approach that enabled us to evaluate whether null results at a group level were due to either a lack of effect in most subjects or significant but inconsistent effects across subjects.

RESULTS

Common Effects for Word and Pseudoword Reading

Reading pseudowords and words increased activity relative to fixation ($p > .05$ corrected for multiple comparisons) in the left cerebellum and in the left posterior inferior temporal (LPIT), left inferior frontal, and bilateral occipital cortices. Trends ($p < .001$ uncorrected) were also found in the left posterior superior temporal and

Table 1. Summary of the Current Neuroimaging Literature on Word and Pseudoword Reading

Word Type Effects	*Price et al., 1996*	*Herbster et al., 1997*	*Rumsey et al., 1997*	*Brunswick et al., 1999*	*Hagoort et al., 1999*	*Fiez et al., 1999*	*Tagamets et al., 2000*	*Paulesu et al., 2000*	*Xu et al., 2001*
Words > pseudowords									
Occipital									
Left anterior fusiform		−36, −30, −24							
Left lingual					−18, −48, 0				
Temporal									
Left middle temporal					−50, −34, −12				
Right middle temporal					54, −47, 7				
Right superior temporal					61, −36, 18				
Frontal									
Left orbital frontal	−22, 24, −8								
Left middle frontal	−26, 46, 28								
Bilateral precentral				58, 0, 44					
Bilateral SMA					−3, −19, 51				
Other									
Left parahippocampal			−26, −42, 8						
Right posterior cingulate					11, −20, 38				
Right thalamus				14, −10, 14					
Pseudowords > words									
Occipital									
Left middle fusiform					−34, −55, −11	−43, −45, −8			
Left middle occipital					−27, −86, 15				
Right posterior fusiform	24, −94, −4						44, −92, −8		
Right middle fusiform					44, −48, −10		44, −64, −28		
Right superior occipital					24, −67, 29				
Right middle occipital					25, −83, 10				

Word Type Effects	Price et al., 1996	Herbster et al., 1997	Rumsey et al., 1997	Brunswick et al., 1999	Hagoort et al., 1999	Fiez et al., 1999	Tagamets et al., 2000	Paulesu et al., 2000	Xu et al., 2001
Temporal									
Left medial temporal	−20, −16, −12								
Left inferior temporal	−48, −62, −4			−42, −54, −20				−52, −60, −20	−46, −66, −10
Left middle temporal					−57, −6, −2				
Left temporo-parietal	−24, −42, 28								
Right inferior temporal	50, −50, −12								32, −76, −14
Right middle temporal	54, −44, 4								
Parietal									
Left supramarginal									−38, −48, 50
Frontal									
Left precentral								−42, 0, 44	
Left superior frontal					−16, −2, 46				
Left middle frontal							−36, 48, −2		
Left inferior frontal		−44, 4, 16		−48, 6, 26	−46, 17, −8	−35, 15, 6		−42, 24, 14	−52, 10, 12
Left insula			−18, 20, −4						
Other									
Right cerebellum					12, −43, −16				10, −72, −46

All studies used positron emission tomography apart from Tagamets, Novick, Chalmers, and Friedman (2000) which used fMRI. Statistical thresholds are *not* corrected for the number of comparisons being made. We report only those activations that survive a threshold of $p < .001$ (uncorrected) apart from Fiez et al. (1999) ($p < .05$, uncorrected).

Table 2. Regions that Showed an Effect of Reading Relative to Fixation Common to Words and Pseudowords

		Reading > Fixation Common to Words and Pseudowords		
		Words and Pseudowords > Fixation	*Pseudowords > Fixation*	*Words > Fixation*
Occipital				
Left fusiform	−36, −74, −24	**7.0**	4.9	4.6
Right fusiform	18, −86, −12	**5.3**	**6.2**	**5.8**
Temporal				
Left posterior inferior temporal	−40, −62, −16	**5.7**	**6.0**	**5.1**
Left posterior superior temporal	−56, −50, 6	4.1	3.2	3.1
Parietal				
Left angular gyrus	−28, −56, 50	4.8	4.9	4.2
Right angular gyrus	34, −54, 52	4.8	4.5	4.5
Frontal				
Left inferior frontal	−42, 16, 32	**5.1**	3.2	3.1
Right inferior frontal	48, 12, 30	4.6	3.9	3.6
Other				
Left cerebellum	−36, −52, −26	**5.2**	4.9	**5.4**
Right cerebellum	32, −68, −24	4.7	**5.3**	3.3

Z scores significant at $p < .05$ (corrected for multiple comparisons) are reported in **bold**.

right inferior frontal cortices, in the bilateral angular gyri, and in the right cerebellum (see Table 2 for details). These results are consistent with previous studies on reading (see Price, 2000 for a review), confirming that subjects were engaged in the task.

Word Type Effects

Pseudowords > Words

Reading pseudowords increased activity relative to both words and fixation ($p > .05$ corrected for multiple comparisons) in the left frontal operculum, the left inferior temporal gyrus, and the right cerebellum (see Figure 2 and upper part of Table 3 for details). There were no interactions with stimulus duration.

Words > Pseudowords

There were no areas where reading words increased activity relative to both pseudowords and fixation ($p > .05$ corrected for multiple comparisons). However, the right superior frontal sulcus, right supramarginal,

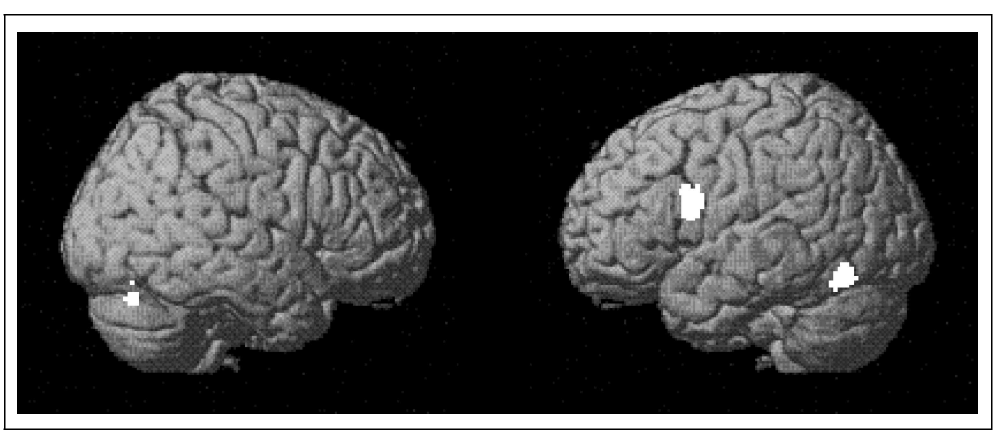

Figure 2. Brain regions that showed more activity for reading pseudowords than words ($p < .05$ corrected for multiple comparisons) (see Table 3 for details).

Table 3. Regions that Showed an Effect of Word Type in the Present Study

		Pseudowords > Words and Fixation		
		Pseudowords > Words	*Pseudowords > Fixation*	*Words > Fixation*
Temporal				
Left posterior inferior temporal	−44, −64, −16	**5.3**	**5.6** (−46, −64, −14, **6.8**)	**5.0** (−46, −66, −12, **6.1**)
Frontal				
Left inferior frontal (pars opercularis)	−48, 8, 22	**5.0**	4.7 (−44, 8, 24, **5.1**)	1.1 (−44, 20, 20, 4.1)
Other				
Right cerebellum	32, −70, −26	**5.1**	4.7 (30, −68, −26, **5.3**)	3.0 (38, −66, −24, 4.1)
		Words > Pseudowords		
		Words > Pseudowords	*Fixation > Pseudowords*	*Fixation > Words*
Occipital				
Left middle occipital	−36, −76, 28	**5.1**	4.2 (−42, −78, 28, **5.7**)	0.7
Parietal				
Right supramarginal	62, −28, 32	**5.5**	**5.0** (64, −28, 34, **5.3**)	3.5
Frontal				
Right postcentral gyrus	56, −18, 24	**5.3**	4.4	1.5
Right superior frontal sulcus	32, 20, 48	**5.0**	4.1 (32, 18, 46, **5.0**)	1.2

Z scores significant at $p < .05$ (corrected for multiple comparisons) are reported in **bold**. It can be seen that effects of pseudowords relative to words were associated with "increases" in activity for both words and pseudowords relative to fixation. On the other hand, effects of words relative to pseudowords were associated with "decreases" in activity for reading pseudowords relative to fixation.

right postcentral, and left middle occipital gyrus were more active for words relative to pseudowords. These effects were not associated with an increase for reading words but a decrease for reading pseudowords relative to fixation (see lower part of Table 3 for details). To explore the possibility that different subjects used different reading strategies, we also looked for effects of reading words > pseudowords at an individual subject level at $p < .05$ (corrected for multiple comparisons) with an extent threshold of 10 voxels. Significant effects of reading words relative to pseudowords and fixation were observed in 7 out of 20 subjects. However, none of these effects was replicated in any of the other subjects (see Table 4 for details).

Duration Effects

Positive Linear Effects

Positive linear effects of stimulus duration were found in the bilateral posterior fusiform and middle occipital regions ($p > .05$ corrected for multiple comparisons). Positive linear trends were also found in the left precentral gyrus and cerebellum ($p < .001$ uncorrected) (see upper part of Table 5). These results are consistent with previous PET findings (Price & Friston, 1997).

Negative Linear Effects

Negative effects of stimulus duration significant at a corrected level were not detected. However, a number of effects significant at $p < .001$ (uncorrected) were found in right lateralized regions (see lower part of Table 5). These largely overlap with the areas that showed negative effects of stimulus duration at $p < .001$ (uncorrected) in Price and Friston (1997).

Quadratic Effects

Quadratic effects, either positive or negative, were not detected even when lowering the statistical threshold to $p < .001$ (uncorrected). The nonlinear dependencies found in Price and Friston (1997) using PET and fixed-effects models were therefore not replicated with fMRI when inferences pertained to the population from which subjects came as opposed to the particular subjects studied.

DISCUSSION

The main aim of the present investigation was to establish whether there were any reliable and consistent differences in the pattern of neural activation evoked by word and pseudoword reading. In previous studies, the data were analyzed using conventional fixed-effect statistical models, which test for average activation across subjects without segregating ''within'' and ''between'' subject variance. This means that significant results at a group level can be found when there are large effects in one or a subset of subjects and no effects in the majority of subjects. Fixed-effect analyses allow one to draw inferences pertaining to the particular group of subjects studied but not to the population from which those subjects came. In contrast, the present investigation used data from a larger number of subjects and a random-effect statistical model that is based on between-subject variance. Random-effect analyses allow one to draw inferences at the population level (see Friston et al., 1999, for a detailed account of fixed- and random-effect analysis). Furthermore, in the present study, we only report and discuss effects that reach levels of significance corrected for the number of comparisons being made. This minimizes false-positive results, which may be another cause of inconsistencies in the previous functional neuroimaging literature. Below, we discuss the main findings of the present study and their implications for cognitive models of reading.

Main Findings

Using a random-effects statistical model and significance thresholds that were corrected for multiple comparisons across the whole brain, we found that reading pseudowords relative to words and fixation increased activation in the left frontal operculum, the LPIT gyrus, and the right cerebellum. In addition, we found an effect of reading words relative to pseudowords in a dorsal region of the left middle occipital cortex and in the right supramarginal, postcentral, and superior frontal areas. Critically, the word effects were due to deactivation for reading pseudowords relative to fixation rather than increased activity for reading words relative to fixation. This raises the possibility that increases for words relative to pseudowords reported by previous studies were due to decreases for pseudowords.

Word type effects due to an increase in activity for reading words relative to pseudowords and fixation were only observed at an individual level. This suggests that intersubject variability may account for some of the inconsistencies in the neuroimaging literature. It should be noted that a number of subject-specific effects of word type were highly significant with Z scores as high as 8.8. Such effects may have an impact on the results at a group level in the context of a fixed-effect analysis, especially in studies that involve a relatively small number of subjects

Table 4. Subject-Specific Effects of Reading Words Relative to Pseudowords Associated with an Increase in Activity for Reading Words Relative to Fixation

	Words > Pseudowords and Fixation			
			Words > Pseudowords	*Words > Fixation*
Subejct 1	Left posterior cingulate	−10, −46, 26	**6.0**	3.1
	Right cerebellum	18, −78, −22	**8.8**	4.3
Subject 4	Left superior temporal sulcus	−38, −58, 28	**7.8**	**5.1**
Subject 5	Right middle frontal	22, 62, 14	**7.3**	**5.6**
	Right circular insular sulcus	46, −10, 20	**6.8**	4.3
	Left anterior cingulate sulcus	−12, 56, 2	**8.4**	**5.2**
Subject 11	Right anterior middle temporal	58, 0, −20	**6.1**	**4.9**
Subject 15	Medial paracentral lobule	2, −38, 64	**5.8**	4.1
	Right superior temporal sulcus	58, −58, 18	**7.4**	**5.7**
Subject 16	Right angular	48, −48, 34	**7.2**	4.6
Subject 18	Right posterior superior temporal	60, −42, 14	**5.6**	3.2
	Right posterior middle temporal	56, −40, 2	**7.0**	4.1

Z scores significant at $p < .05$ (corrected for multiple comparisons) are reported in **bold**. Although some effects of words relative to pseudowords and fixation were highly significant, there were no replications across subjects.

Table 5. Regions which Showed Either Positive or Negative Linear Effects with Stimulus Duration

	Positive Linear Effects of Duration		
	Positive Linear		*Reading 1000 msec > Fixation*
Occipital			
Left posterior fusiform	−14, −94, −14	**5.3**	**5.0**
	−34, −80, −12	**5.2**	4.8
Right posterior fusiform	16, −90, −10	**5.1**	**5.0**
Left middle occipital	−32, −86, 2	**5.2**	3.8
Right middle occipital	26, −94, 10	**5.0**	4.7
Frontal			
Left precentral	−56, 6, 38	4.2	3.5
Other			
Left cerebellum	−34, −50, −24	4.2	4.4
	Negative Linear Effects of Duration (Trends)		
	Negative Linear		*Reading 200 msec > Fixation*
Temporal			
Right posterior middle temporal	62, −54, 0	4.2	2.5
Right anterior middle temporal	48, −26, −16	4.6	*ns*
Parietal			
Right angular gyrus	54, −56, 36	4.5	*ns*
Right SMA	36, 6, 60	4.0	2.5
Frontal			
Right middle frontal	44, 40, 22	3.9	2.4
Other			
Right cingulate	6, −28, 46	3.6	*ns*
Right putamen	32, −4, −4	3.9	2.4
Right cerebellum	22, −46, −30	4.6	*ns*
Left cerebellum	−32, −74, −30	4.2	*ns*

Z scores significant at $p < .05$ (corrected for multiple comparisons) are reported in **bold**.

(i.e., up to 8). In contrast, the random-effect analysis we used here protected us from significant results due to large effects in one or a few subjects only.

Our experimental design also allowed us to explore whether the effect of word type was modulated by stimulus duration. Although we found highly significant main effects of stimulus duration, which were broadly consistent with those reported in Price and Friston (1997), there were no significant interactions between stimulus duration and word type (this study) and no evidence for an interaction between stimulus rate and word type (see Mechelli, Friston, & Price, 2000). Thus, the present data do not support the hypothesis that the effect of word type is modulated by experimental parameters such as stimulus rate and duration (see Figure 3).

Implications for Cognitive Models of Reading

The results of this study, and previous studies of word and pseudoword reading, have not yet provided evidence for one cognitive model over the others. This is because, as indicated in the Introduction, these models do not make clear-cut predictions at the neural level. For example, a double dissociation in the activation patterns for reading words and pseudowords could either reflect (a) differential demands on lexical and sublexical routes; or (b) the degree to which semantics and phonology is activated for words and pseudowords, respectively. Furthermore, since pseudowords and words differ in familiarity as well as lexicality, interpreting word type effects requires reference to other studies that have manipulated lexicality or familiarity independently of word type. We therefore interpret the effects we see for pseudowords relative to words in reference to the results of other neuroimaging studies that have seen activation in the same areas.

The most robust effects for pseudowords relative to words and fixation were observed in three areas (the left frontal operculum, the LPIT cortex, and the right cerebellum). Similar effects for pseudowords relative to words have been reported in the left frontal operculum by Xu et al. (2001), Brunswick et al. (1999), Fiez et al. (1999), Hagoort et al. (1999), and Herbster et al. (1997); in the LPIT by Xu et al. (2001), Brunswick et al. (1999), and Price et al. (1996); and in both the LPIT and the frontal operculum by Paulesu et al. (2000). All three areas are also activated during lexical retrieval tasks irrespective of stimulus modality and even in the absence of orthographic input (see Price, 2000 for a review). For instance, in the visual domain, they are activated for picture, letter, and color naming (Price & Friston, 1997); in the auditory domain, they are activated for repetition (Noppeney & Price, 2002) and word generation (Frith, Friston, Liddle, & Frackowiak, 1991); and in the tactile domain, they are activated when blind subjects read Braille (Büchel, Price, & Friston, 1998). Thus, increased activation for pseudoword relative to word reading corresponds to that found for lexical retrieval. Previous studies have suggested that pseudowords may increase the demands on lexical processing because there is no semantic representation available (Fiez et al., 1999; Price et al., 1996). However, this conclusion does not allow us to determine whether there are separate neural systems involved in lexical and sublexical orthographic to phonological mapping. For instance, the common activation pattern we observe for words and pseudowords might include a sublexical processing system that is equally activated by words and pseudowords (e.g., in the left posterior superior temporal cortex). It is also possible that sublexical and lexical processes engage different neuronal populations within the same anatomical region.

While the effects in the LPIT and the frontal operculum are relatively consistent with the literature, it can be noted that greater activation in the right cerebellum for pseudowords relative to words was not reported in any of the studies listed in Table 1. One possible explanation is that, in this region, the effect of word type is subtle but highly consistent across subjects. This would result in significant activation when the effect size is compared

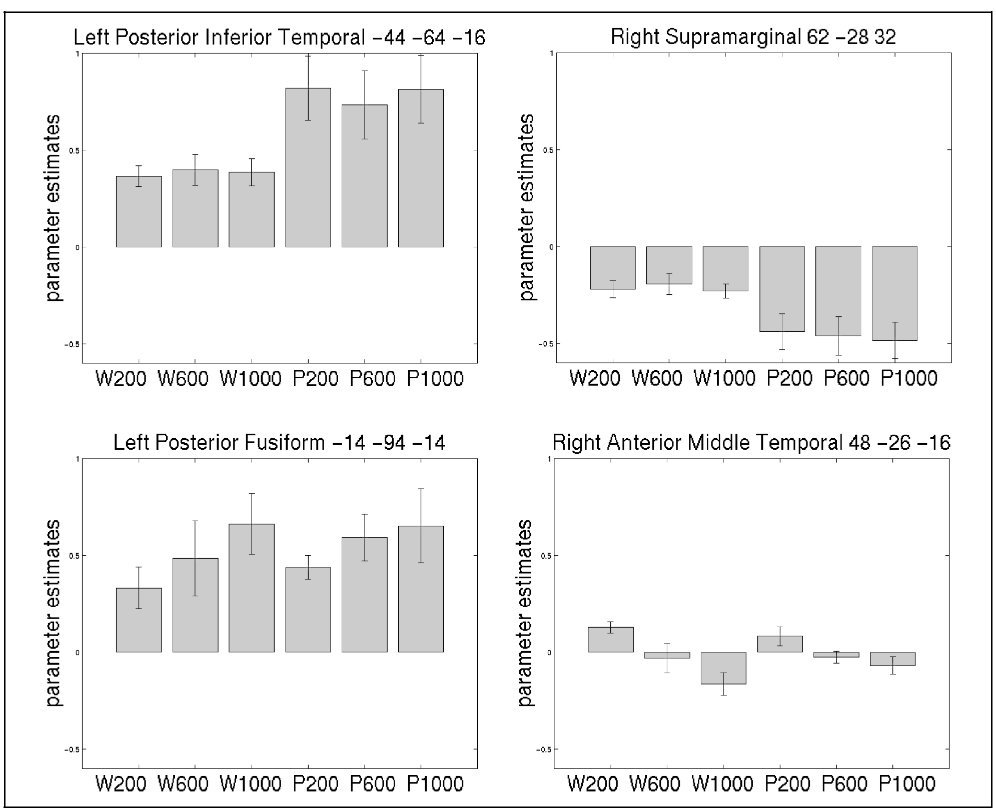

Figure 3. Parameter estimates (averaged across subjects) for the height of the hemodynamic response during word (W) and pseudoword (P) reading with stimulus durations of 200, 600, and 1000 msec. Vertical bars indicate standard errors. The scale is kept constant (−0.6 to 1) in order to illustrate the relative effects in each area. However, this de-emphasizes the smaller effects. Four main response profiles were identified: increases for reading pseudowords relative to words and rest (e.g., left inferior temporal); decreases for reading pseudowords relative to words and rest (e.g., right supramarginal); linear increases with stimulus duration (e.g., left posterior fusiform); and linear decreases with stimulus duration (e.g., right anterior middle temporal).

against intersubject variability (i.e., in a random-effect analysis) but not when the effect size is averaged across subjects and compared against the within-subject variability (Friston et al., 1999).

With respect to the deactivations, we observed for reading pseudowords relative to fixation, we note that localized task-induced decreases in activity are a relatively frequent finding in functional neuroimaging (see Mazoyer et al., 2001; Binder et al., 1999; Shulman et al., 1997) but remain poorly understood. Binder et al. (1999) suggest that rest/fixation is a semantic condition, therefore deactivation for pseudoword but not word reading may reflect an interruption of semantic activity. However, the areas we see deactivated for pseudoword reading (right superior frontal sulcus, right supramarginal, right postcentral, and left middle occipital gyrus) do not correspond to those associated with semantic processing. An alternative perspective (see Gusnard & Raichle, 2001) is that deactivations occur in areas that are not involved in task performance and this facilitates the processing of task-relevant information. Within this framework, deactivations for pseudowords relative to words might reflect the relative demands on the reading system.

Finally, the lack of consistent activations for words relative to pseudowords and fixation needs to be addressed. Here there are a number of possible explanations. For instance, words may engage the same neuronal components as pseudowords with word-specific effects emerging only in the strength of functional connections. This may not be revealed by classical subtraction paradigms but requires tests of functional or effective connectivity such as the application of structural equation modeling (e.g., Mechelli et al., in press; Horwitz, Friston, & Taylor, 2000; Horwitz, Rumsey, & Donohue, 1998; Büchel & Friston, 1997; McIntosh & Gonzalez-Lima, 1994). Alternatively, if word and pseudoword processing is distinguished by differences in the timing of activation, this will not be detected when activation is summed over time. For example, onset or peak activation at the same location may occur at different times for words and pseudowords (Henson, Price, Rugg, Turner, & Friston, 2002; Simos et al., 2002) or one word type might evoke a transient response while the other evoked more sustained activity at a lower amplitude. In summary, there are many different ways that word-specific effects could be expressed at the neural level but the imaging techniques we (and others) currently have available may not be sufficiently sensitive to detect them.

Conclusions

In this article, we identify consistent and inconsistent effects of word type across subjects, and distinguish between effects associated with increases and decreases in activity relative to fixation. We find that reading words and pseudowords activate a common set of areas and, within this system, pseudowords increase activation in areas previously linked to lexical retrieval. In contrast, we only find consistent effects of reading words relative to pseudowords that are due to decreases for pseudowords rather than increases for words relative to fixation. Word-specific activations relative to fixation are observed at the individual level but with no consistency over subjects. We conclude that reading pseudowords enhances the demands on lexical retrieval. Our results also highlight the importance of using one or more baselines in order to qualify word type effects, and the problems associated with studies that include only a limited number of subjects and use fixed-effect analyses.

Further experiments are required to investigate (i) the functions of areas that activate in common to words and pseudowords (e.g., the function of the left superior temporal sulcus during reading); (ii) word type dependent changes in functional connectivity; (iii) the effect of word type on the timing of activations; and (iv) explanations for the intersubject variability.

METHODS

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

Subjects

Informed consent was obtained from 20 right-handed volunteers (7 males), aged between 20 and 38 (with a mean age of 26), with English as their first language.

Design and Task

Data were acquired in two different experiments (7 and 13 subjects). Each alternated blocks of words and pseudowords with fixation (to a cross in the middle of the screen). Subjects were instructed to read the words or pseudowords silently as soon as they appeared on the screen. This silent reading paradigm was chosen in order to minimize task-induced effects and avoid the activation of temporal regions caused by subjects processing their own voice (Price et al., 1996). In the first experiment (7 subjects), stimulus duration was constant (600 msec) and stimulus rate varied (20, 40, or 60 words per minute). This experiment included data from the six subjects reported in Mechelli et al. (2000) and an additional subject performing the same paradigm. Effects of word type were not reported by Mechelli et al., as the aim of that article was to investigate whether the effects of stimulus rate were consistent for words and pseudowords and across scanning modalities (i.e., PET and fMRI). In the second experiment (13 subjects), stimulus rate was held constant (40 words per minute) and stimulus duration was manipulated (200, 600, and 1000 msec).

Stimuli were presented in blocks with each of the six experimental conditions repeated five times in a counterbalanced order across subjects. Each block lasted 21 sec and was followed by 16 sec fixation. An eye-tracker was used to monitor the eye movements of the subjects, in order to ensure that they kept their eyes open and attended to the stimuli.

Stimuli

Stimuli were composed of four, five, or six letters. Words were matched for frequency (Kucera & Francis, 1967), length, and number of syllables between blocks and the grapheme–phoneme relationships were regular. Pseudowords were created from these words by changing the onset, the internal consonants, or the coda. Examples of the words and corresponding pseudowords include: toast–noast, letter–lenner, and lemon–lenos. Words and pseudowords were matched for bigram frequency between blocks.

Scanning Technique

A 2-T Siemens VISION system (Siemens, Erlangen, Germany) was used to acquire both T_1 anatomical volume images ($1 \times 1 \times 1.5$ mm voxels) and T_2*-weighted echo-planar images (64 by 64, 3 by 3 mm pixels, TE = 40 msec) with BOLD contrast. Each echo-planar image comprised 35 axial slices 1.8-mm thick with a 1.2-mm slice interval, giving a resulting resolution of 3 mm. For each subject involved in either experiment, a total of 366 volume images were taken continuously with an effective repetition time (TR) of 3.15 sec/volume, the first six (dummy) volumes being discarded to allow for T_1 equilibration effects. Stimulus presentation was arranged so that every 90 msec of peristimulus time was sampled equally over the session (see Price, Veltman, Ashburner, Josephs & Friston, 1999).

Data Analysis

Data were analyzed with statistical parametric mapping (SPM99:Wellcome Department of Imaging Neuroscience, London, UK. http//www.fil.ion.ucl.ac.uk), running under Matlab5.3 (Mathworks, Sherbon, MA, USA). All volumes from each subject were realigned using the first as reference and were resliced using sinc interpolation, adjusting for residual motion-related signal changes. The functional images were spatially normalized (Friston, Ashburner, et al., 1995) to a standard MNI-305 template (MNI, ICBM NIH P-20 project) using nonlinear basis functions. This transformation was also applied to the realigned structural T_1 volume. Functional data were spatially smoothed with a 6-mm full width half maximum isotropic Gaussian kernel, to compensate for residual variability after spatial normalization and to permit application of Gaussian random-field theory for corrected statistical inference (Friston, Holmes, et al., 1995).

Statistical Analysis

Data were analyzed in a subject-specific fashion, with each of the six conditions (Stimulus type $\times$ Rate or duration) modeled separately in reference to a boxcar waveform convolved with a synthetic hemodynamic response function (HRF). The data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 156 seconds. Differences in global flow within subjects were removed using proportional scaling. However, given the possibility that the local regional changes might confound the estimate of global signal and lead to ''artifactual'' deactivations, we replicated the statistical analysis without global normalization. The deactivations did not appear to be artifacts. Thus, the results reported and discussed below refer to the statistical analysis performed using proportional scaling.

We identified the effects of (i) reading relative to fixation common to words and pseudowords (by contrasting reading words and pseudowords relative to fixation) and (ii) word type (by contrasting words relative to pseudowords and vice versa) in 20 subjects. In addition, a parametric analysis was performed that employed a nonlinear regression including all stimulus durations (Büchel, Wise, Mummery, Poline, & Friston, 1996). This allowed the relationship between neuronal activity and stimulus duration to be investigated in the 13 subjects who performed the duration study. (i) Positive linear dependencies, (ii) negative linear dependencies, (iii) positive quadratic (U-shaped) dependencies, and (iv) negative quadratic dependencies (inverted U-shaped) were identified for both words and pseudowords, for words relative to pseudowords, and for pseudowords relative to words independently. The effects of stimulus rate were not addressed here because they have been examined in a previous study (Mechelli et al., 2000).

The contrast images from each of the analyses at an individual subject level were entered into one-sample t tests to permit inferences about condition effects across subjects (i.e., a random-effects analysis). The t images for each contrast at the second level were subsequently transformed into statistical parametric maps of the Z statistic. Unless otherwise indicated, we report and discuss regions that showed significant effects at $p < .05$ (corrected for multiple comparisons) with an extent threshold for each cluster of 15 voxels at $p < .001$ (uncorrected).

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The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2002-1135N.

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