

Conjoint and Extended Neural Networks for the Computation of Speech Codes: The Neural Basis of Selective Impairment in Reading Words and Pseudowords

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The computation of speech codes (i.e. phonology) is an important aspect of word reading. Understanding the neural systems and mechanisms underlying phonological processes provides a foundation for the investigation of language in the brain. We used high-resolution three-dimensional positron emission tomography (PET) to investigate neural systems essential for phonological processes. The burden of neural activities on the computation of speech codes was maximized by three rhyming tasks (rhyming words, pseudowords and words printed in mixed letter cases). Brain activation patterns associated with these tasks were compared with those of two baseline tasks involving visual feature detection. Results suggest strong left lateralized epicenters of neural activity in rhyming irrespective of gender. Word rhyming activated the same brain regions engaged in pseudoword rhyming, suggesting conjoint neural networks for phonological processing of words and pseudowords. However, pseudoword rhyming induced the largest change in cerebral blood flow and activated more voxels in the left posterior prefrontal regions and the left inferior occipital-temporal junction. In addition, pseudoword rhyming activated the left supramarginal gyrus, which was not apparent in word rhyming. These results suggest that rhyming pseudowords requires active participation of extended neural systems and networks not observed for rhyming words. The implications of the results on theories and models of visual word reading and on selective reading dysfunctions after brain lesions are discussed.

Introduction

Behavioral research on word reading has shown that the computation of speech codes plays a crucial role in word recognition (Van Orden, 1987; Perfetti, 1985; Perfetti *et al.*, 1992; Share and Stanovich, 1995). Phonological decoding seems to influence not only word reading in alphabetic writing systems, but also in other writing systems (Perfetti *et al.*, 1992; Frost, 1994; Sasanuma and Karalyn, 1995; Tan *et al.*, 1995). In addition, theories and models of visual word recognition have proposed similar mechanisms for reading words and pseudowords (i.e. pronounceable nonwords) (Glushko, 1979; Van Orden *et al.*, 1990; Plaut *et al.*, 1995; Coltheart and Haller, 1993; Seidenberg *et al.*, 1994). Although these theories and models may differ in their specifics as well as in design principles (e.g. symbolic versus distributed representations), there is a general agreement that word and pseudoword reading involve mapping orthography (e.g. letters) to phonology by assembling sublexical phonological codes (e.g. graphemes and phonemes) (Berent and Perfetti, 1995).

At the same time, both behavioral and neuropsychological studies have consistently found latency differences in naming words and pseudowords. Behavioral results have shown that in general, pseudoword naming takes more time than word naming (Forster and Chambers, 1973; Frederiksen and Kroll, 1976; Lukatela *et al.*, 1989; Besner *et al.*, 1990; Lukatela and Turvey, 1993; Stone and Van Orden, 1993). A common explanation for

this latency difference is that words afford a higher level of orthographic familiarity due to frequency of use than pseudowords or unfamiliar low-frequency words and, therefore, mapping orthography to phonological codes is more automatic and less resource demanding for words relative to pseudowords (Seidenberg and McClelland, 1989; Van Orden and Goldinger, 1994; Plaut *et al.*, 1995). Consequently, under similar experimental conditions, word reading is faster and more accurate than pseudoword reading.

An alternative account for the differences in word and pseudoword reading is that relative to pseudowords, phonological codes for words may be activated at lexical (i.e. word) rather than sublexical (e.g. graphemes) level (Coltheart, 1978). This is partly because words have lexical representations in the language system and pseudowords do not. Thus, the computation of speech codes for words and pseudowords may utilize different mechanisms. For familiar words, orthography may be directly mapped onto lexical phonology (Morton, 1982; Rumelhart and McClelland, 1982; Besner and Hildebrandt, 1987; Grainger, 1990; Baluch and Besner, 1991; Sebastian-Galles, 1991; Seidenberg *et al.*, 1994; Share, 1995).

Evidence from neuropsychological studies also suggests that brain lesions may impair the ability to read pseudowords more than the ability to read words (Alexander *et al.*, 1992; Shallice, 1988). On the other hand, impairment in reading regularly spelled words almost always coincides with poor ability in reading pseudowords (Beauvois and Derouesne, 1979; Shallice and Warrington, 1980; Warrington, 1981; Patterson, 1982; Derouesne and Beauvois, 1985). For acquired phonological dyslexics, pseudoword reading is almost always substantially worse than word reading (Fiez and Petersen, 1998; Shallice, 1988). These patients, however, often have little difficulty in reading letters, a phenomenon often interpreted as intact visual perceptual ability (Shallice, 1988). The differences and similarities in reading words and pseudowords may partly reflect differences in neural systems crucial for the computation of phonology for words and pseudowords in addition to shared processes. Identifying differences in the functional anatomy and neural networks of language processes may, in turn, lend insight to refining models of word perception and address whether there are common versus separate mechanisms for reading words and pseudowords.

The goal of this study was to provide evidence to answer three related questions about phonological processing in the brain: (i) Are there distinct epicenters of neural activity associated with the phonological processing of words and pseudowords? (ii) Are the epicenters for phonological processing lateralized? (iii) Are the epicenters for phonological processing topographically consistent with findings in brain lesion studies? A few previous neuroimaging studies have attempted to address these questions (Petersen *et al.*, 1988; Demonet *et al.*, 1992;

Price *et al.*, 1996; Price *et al.*, 1997; Rumsey *et al.*, 1997; Hagoort *et al.*, 1999).

Price *et al.* reported a PET study investigating automatic activation of language functions with words and pseudowords (Price *et al.*, 1996). They asked subjects to perform a non-linguistic feature detection task with visually presented letters while either words or pseudowords were presented simultaneously in the visual field. Their results showed that both word and pseudoword conditions activated similar brain regions and 'pseudowords activate the language network more strongly than words' (p. 68). Based on these results they concluded that phonological processing of words and pseudowords involve similar neural networks. However, Price *et al.* used an implicit nonlinguistic task for measuring the effects of word and pseudoword stimuli and did not try to separate the contribution of various processing components associated with stimulus presentation characteristics. In addition, they reported significant activation in many cortical regions, of which only a few were common to both word and pseudoword stimuli. Rumsey *et al.*, using positron emission tomography (PET) imaging techniques, found that phonological processing for pseudowords showed greater activation than for real words although similar brain regions were involved for both word and pseudoword stimuli (Rumsey *et al.*, 1997). However, because their 'pseudowords differed substantially from real words' in phonotactic structures (p. 743), and because their behavioral data suggested that the pseudoword condition was significantly more difficult than the word condition, the cause of the difference in activation between the two conditions is difficult to determine. The activation difference could be due to either differences in stimuli and the level of difficulty between the word and pseudoword conditions or in the qualitative difference between word and pseudoword reading in general. Thus, questions remain concerning the topographical differences in the neural systems for reading words and pseudowords, especially those induced by the computation of speech codes.

Other imaging studies using phonological tasks have also reported common brain regions corresponding to phonological processing (Fiez and Petersen, 1998). However, these studies also showed the participation of additional and differing cortical regions (Petersen *et al.*, 1988; Demonet *et al.*, 1992; Price *et al.*, 1997). Differences among the results of studies may be partly attributable to variations in experimental tasks (e.g. rhyming with pictures versus syllable segmentation), baseline conditions (e.g. rest versus feature detection or word repetition), presentation rate (>2 s for most imaging studies), and the degree of stimulus constancy across experimental conditions (Petersen *et al.*, 1988; Bookheimer *et al.*, 1995; Price *et al.*, 1997, 1998; Paulesu *et al.*, 2000). Differences among studies may also indicate a failure to isolate the phonological function (or processing component) from other cognitive functions unique to various experimental tasks. In fact, it can be difficult to separate one specific cognitive function, such as phonology, from other cognitive functions that are engaged by the same experimental task. The difficulty partly lies in the limitations of neuroimaging techniques (e.g. low temporal resolution) and to a great extent, in the complex automatic interactions and functional interdependencies among various cognitive systems necessary for performing even a simple task such as word reading (Van Orden and Paap, 1997). However, as in any other science, confidence in neuroimaging findings may only rise when evidence from imaging and neuropsychological studies using various experimental techniques (Fiez and Petersen, 1998; Posner and Carr,

1992) converge on a consistent result. The current study was intended to contribute in such a way to the literature on phonological processing.

In this study, we used word and pseudoword (i.e. pronounceable nonwords) rhyming tasks to maximize the burden of neural activities in computing phonological codes. While keeping the perceptual input relatively constant, two baseline conditions minimized the computation of speech codes (see Materials and Methods for detailed discussion). The interpretation of epicenters of neural activities was based on the statistically significant results of subtractive contrasts between these two types of tasks.

Methodologically, this study differs in at least three respects from most previous imaging studies of phonological processing. First, all the critical conditions required subjects to perform a silent rhyming task. Previous studies often involved multiple different cognitive tasks (e.g. rhyming and meaning judgment) within a single experimental session (Petersen *et al.*, 1988; Petersen and Fiez, 1993; Shaywitz *et al.*, 1995; Pugh *et al.*, 1996). We chose to include a single task for all experimental conditions to minimize task-induced effects between conditions and avoid cross-task interference (Carr and Dagenbach, 1990). Second, the stimuli used in this experiment were kept relatively constant across experimental conditions (see Materials and Methods for detailed description of the stimuli). Third, and most important, is that in the current experiment, the stimulus duration was 500 ms and the interstimulus interval was 600 ms. Many previous studies adopted much slower presentation rates, most exceeding 2–4 s (Gabrieli *et al.*, 1996; Pugh *et al.*, 1996; Price *et al.*, 1997). Behavioral studies using eye-tracking techniques have repeatedly demonstrated that, on average, reading a four- to six-letter word takes only ~250 ms or less (Carpenter and Just, 1983; Rayner and Pollatsek, 1989). Long exposure duration of stimuli, and slow presentation rates are likely to induce processes or recruit cognitive systems that are not directly related to word recognition.¹ Therefore, differences in previous findings regarding the functional anatomy of phonology may also be a consequence of insufficient control over stimulus duration and presentation rate. Our take on stimulus presentation in blood flow studies is that presentation duration and rate should be sufficient to allow, at least, above chance performance. Both insufficient and excessive exposure duration and rate may promote the participation of cognitive systems and brain regions that are not essential for language processing.

Materials and Methods

Subjects

Twelve right-handed, healthy, normal adult volunteers (six males and six females) were paid to participate in the experiment at the National Institutes of Health in the United States. The study was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Strokes. All subjects signed an informed written consent in accordance with the Declaration of Helsinki printed in the *British Medical Journal* (18 July 1964). Edinburgh Handedness Inventory laterality quotients (Oldfield, 1971) indicated that all the subjects were strongly right-handed. The average age for both the males and females was 27 years (range: 24–29 for the males and 23–34 for females). All subjects had college-level education. Two males and four females were attending graduate schools. They all had normal neurological examinations and structural brain imaging using magnetic resonance imaging (MRI).

PET Techniques

All scans were performed on a GE Advance scanner using H₂¹⁵O radioactive isotope. Acquisition was in three-dimensional mode with 35 axial slices (in-plane resolution FWHM = 6 mm in all directions). Each 60 s

Table 1
Planned statistical contrasts

Planned contrasts	Expected activation
1 Pseudoword rhyming – color-matching with letters (PWR–CML)	phonology
2 Real-word rhyming – color-matching with letters (RWR–CML)	phonology and meaning
3 Alternate-case rhyming – color-matching with letters (ACR–CML)	phonology, meaning and perceptual familiarity
4 Real-word rhyming – pseudoword rhyming (RWR–PWR)	meaning
5 Alternate-case rhyming – real-word rhyming (ACR–RWR)	perceptual familiarity
6 Alternate-case rhyming – pseudoword rhyming (ACR–PWR)	perceptual familiarity and meaning
7 Color-matching with letters – color-matching with symbols (CML–CMS)	effect of letter perception

single frame began automatically following a step increase in the scanner true count rate. Each participant received 10 injections of $H_2^{15}O$ with 10 mCi each. The interscan interval was 10 min. $H_2^{15}O$ was administered through a venous line in subjects' right arm. No arterial lines were used. A thermoplastic mask was placed around subjects' head to reduce head motion.

Stimuli were presented on a computer monitor interfaced with an IBM computer using the commercial experimental software MEL2 produced by Psychology Software Tools, Inc. The viewing screen was placed away from the participant forming $\sim 2^\circ$ of visual angle of the stimuli. Subjects' behavioral responses to the stimuli were recorded through a response cable interfaced with a serial response-box linked to the computer. All responses were made with the left hand.

Material

The experiment included five conditions, three of which required subjects to perform a rhyming task with either real words (RWR, e.g. 'night'), pseudowords (PWR, e.g. 'pight'), or words with alternate letter case (ACR, e.g. 'NiGht'). Including the ACR condition allowed us to estimate the extent to which orthographic familiarity of printed words contributes to processing demands and brain activation. The other two conditions were baseline controls involving a color-matching task. In one of the baseline conditions, stimuli were scrambled letter strings (i.e. color-matching with letters [CML], e.g. 'gnhti') of words presented in the rhyming conditions. In the other baseline condition, stimuli contained only nonlinguistic symbols (i.e. color-matching with symbols [CMS], e.g. ')\ { [/') which were matched to the number of letters in the stimuli used in the other conditions. Stimuli were kept constant across conditions except that the CMS condition used non-linguistic symbols and that words and pseudowords differed only by the initial consonant(s). The purpose of keeping stimuli and task relatively constant was to minimize differences between conditions in terms of visual features, decision responses and working memory load.

Design and Procedure

Stimuli were presented in blocks of trials with one experimental condition per block. Each block had 90 trials which lasted for 1 min and 40 s. The stimuli were presented one at a time at a rate of 1100 ms each. Stimulus presentation duration was 500 ms. In the rhyming conditions, subjects were instructed to press the response button as quickly as they could if the current stimulus display rhymed with the previous one. In the two baseline conditions, the subjects' task was to make a response if the current stimulus display and the previous one both had a yellow colored segment (i.e. a yellow letter in the condition with letter strings or a yellow symbol in the symbol condition). The same color segments also appeared in the rhyming conditions. The maximum number of correct responses was 10% of all the trials in a block.

Each presentation block began with the name of the condition followed by a 10 s countdown prior to stimulus presentation. For all blocks, stimulus presentation started ~ 10 s before the administration of $H_2^{15}O$.

Table 2
Mean accuracy and response latencies of the behavioral responses

Sex		Condition				
		CML	PWR	RWR	ACR	CMS
Male	Acc (%)	99 (1)	76 (5.5)	79.2 (7.2)	76 (4.1)	100 (0)
	RT (ms)	514 (27)	738 (35)	723 (35)	731 (37)	515 (42)
Female	Acc (%)	98 (1.3)	74 (3.8)	82.3 (4.4)	75 (4)	100
	RT (ms)	462 (37)	680 (25)	669 (46)	693 (36)	481 (49)

CML, color matching with letters; PWR, pseudoword rhyming; RWR, real-word rhyming; ACR, alternate-case rhyming; CMS, color rhyming with symbols; Acc, accuracy; RT, response time. The numbers in parenthesis are standard errors (in milliseconds for RT and percentage for accuracy).

Data Transformation and Analysis

Images were reconstructed with a transverse Hanning filter and an axial ramp filter. The reconstructed images had a voxel size of $2 \times 2 \times 4.25$ mm. Data were analyzed with the statistical parametric mapping method using SPM97 software and ANCOVA (Friston *et al.*, 1995; Turner *et al.*, 1998). All images were normalized onto the PET template brain created by the Montreal Neurological Institute (MNI) prior to statistical contrasts. Each image was smoothed to account for the variation in normal gray anatomy using Gaussian filter (FWHM = 12 mm³). In the standard space, each voxel size was 2 mm³. Statistical contrasts were performed using the *t*-statistic (under the null hypothesis) in SPM97 for male and female groups and for the two groups combined. Table 1 summarizes the planned statistical contrasts of the study.

Results

Behavioral Data

Table 2 summarizes the behavioral response results. On average, analysis of variance (ANOVA) with experimental condition (five levels) as a within subject factor and gender (two levels) as a between subject factor showed a main effect of condition both in response time (RT) and accuracy, $F(4,20) = 83$, $MSE = 1968$, $P < 0.0001$; $F(4,20) = 24.4$, $MSE = 58.7$, $P < 0.0001$. *Post-hoc* contrasts using a Bonferroni correction with a α at 0.05 revealed that the three rhyming conditions (i.e. rhyming words, pseudowords and words with alternate letter case) differed significantly from the two baseline conditions both in RTs and accuracy. Subjects performed significantly faster and more accurate in the baseline conditions than in the rhyming conditions. However, the rhyming conditions did not differ from each other and neither did the baseline conditions. The differences in performance may reflect differences in the amount of cognitive effort necessary for these tasks or distinctions in which components of a neural system was engaged in performing these tasks (see below).

In addition to the main effect of condition, there was also a significant main effect of gender in RTs, $F(4,20) = 16.9$, $MSE = 1951$, $P < 0.001$. The mean RT (597 ms) for the females was significantly shorter than that for the males (644 ms). However, there was no gender difference in response accuracy ($F < 1$). There were also no significant two-way interactions.

Activation Data

All activations in the planned contrasts were obtained using a conservative height threshold ($P = 0.001$) and a spatial correction ($P = 0.05$). Brain regions are considered to be epicenters of neural activities if the activation at the cluster level survived the threshold criteria. Table 3 summarizes the overall activation loci for males, females and the two groups combined. Only contrasts 1–3 (i.e. PWR–CML, RWR–CML and ACR–CML) illustrated in Table 1 survived the threshold criteria. No clusters or voxels in contrasts 4–7 survived the threshold criteria. This was true for

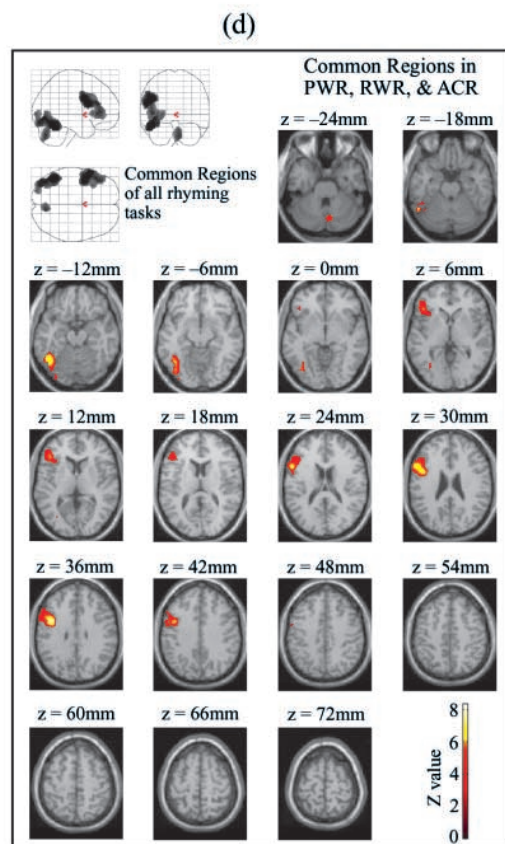
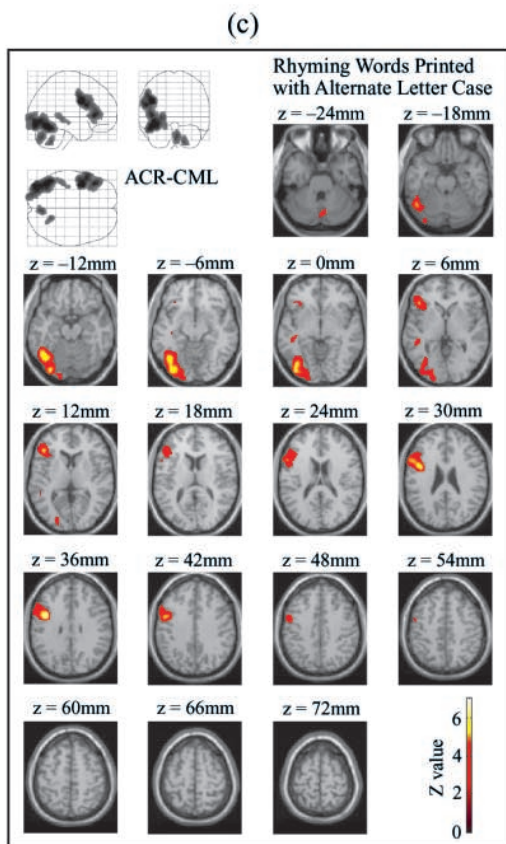
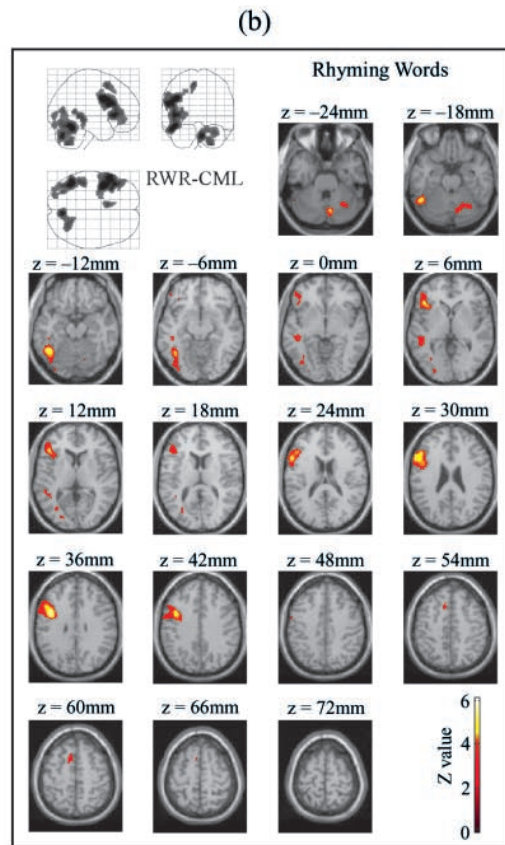
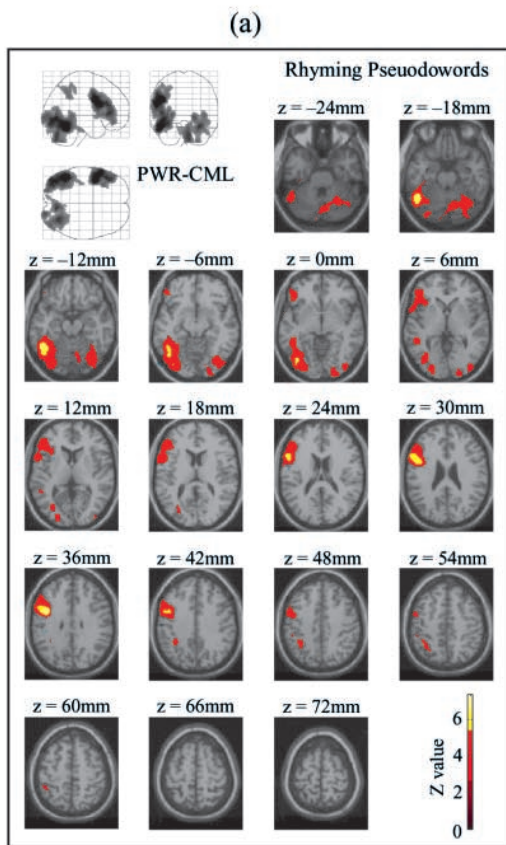


Table 3

Significantly activated brain regions and group average rCBFs during word and pseudoword rhyming relative to the baseline Control (i.e. feature search with letters)

Regions	Coordinates of the peak voxel in a cluster							
	L/ R	Group	PWR-CML	rCBF delta	RWR-CML	rCBF delta	ACR-CML	rCBF Delta
			<i>x y z</i> (Z)	(PWR-CML)	<i>x y z</i> (Z)	(RWR-CML)	<i>x y z</i> (Z)	(ACR-CML)
Cerebellum	R	G	32 -68 -20 (5.6)	3.4	10 -72 -34 (5)	3.3	4 -72 -36 (5)	3
	R	M	12 -72 -38 (4.9)		2 -68 -38 (4.9)		10 -70 -22 (4.2)	
	R	F	-----		-----		6 -72 -28 (4.5)	
Cingulate gyrus	L	G	-----	-----	-----	-----	-----	-----
	L	M	-----		-----		-----	
	L	F	-8 14 50 (4.9)		-6 12 56 (4.2)		-6 10 56 (4.2)	
Mid-temporal gyrus	L	G	-----	-----	-48 -40 0 (4.3)	2.7	-46 -34 -2 (4.2)	-----
	L	M	-----		-----		-----	
	L	F	-----		-46 -34 -2 (4.9)		-46 -34 -2 (5)	
Inferior temporal-occipital junction	L	G	-48 -54 -14 (6.4)	5.9	-44 -56 -16 (5.6)	4.8	-42 -66 -16 (6.2)	5.5
	L	M	-48 -74 -10 (6)		-----		-32 -86 -18 (6.1)	
	L	F	-46 -54 -18 (5.5)		-42 -56 -16 (4.3)		-36 -62 -14 (5.1)	
Posterior-prefrontal cortex	L	G	-44 4 28 (7.4)	6.6	-42 4 30 (6.1)	4.5	-42 4 30 (7)	5.6
	L	M	-42 4 30 (6)		-42 4 32 (4.7)		-42 4 30 (5.2)	
	L	F	-42 2 28 (6.1)		-56 12 20 (5.1)		-42 2 28 (5.9)	
Supramarginal gyrus	L	G	-34 -50 38 (4.2)	3.4	-----	-----	-----	-----
	L	M	-----		-----		-----	
	L	F	-----		-----		-----	

The coordinates represent peak voxels. PWR, pseudoword rhyming; RWR, word rhyming; ACR, rhyming words with alternate case. L, left hemisphere; R, right hemisphere; G, group (i.e. males and females combined); M, male; F, female. rCBF, regional cerebral blood flow. The rCBF delta was estimated by subtracting the amount of rCBF in the baseline condition (i.e. CML) from that in the experimental condition after the global tissue activity was normalized to 50 ml/min/100 ml tissue. Only the rCBF delta in group results are reported here.

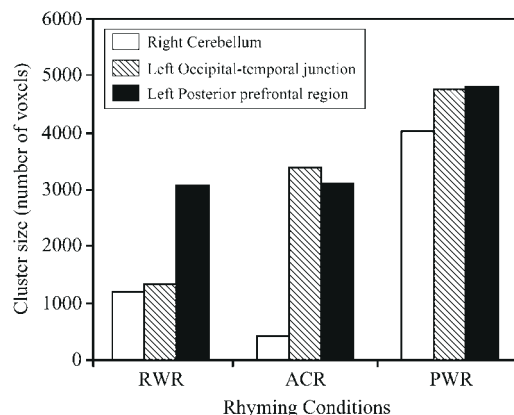


Figure 2. Average (male and female combined) numbers of voxels in three brain regions in rhyming with words (RWR), words with alternate letter case (ACR), and with pseudowords (PWR).

contrasts 4, 6 and 7 (i.e. RWR-PWR, ACR-PWR and CML-CMS) even with a less conservative threshold (i.e. a height threshold of $P = 0.001$ [uncorrected]). However, with the less conservative threshold, contrast 5 (ACR-RWR) showed additional activation, primarily in the occipital lobe (Brodmann areas 18 and 19) (see Fig. 3).

Figure 1a-d shows the group data averaged across all subjects. Relative to the baseline conditions, rhyming words and pseudowords revealed strong activation in the left posterior mid and inferior prefrontal gyri (i.e. Brodmann area 9 and Broca's area), and left inferior occipital-temporal junction (LIOTJ) (see Fig. 1).

Figure 1. (a-c) Results of the three contrasts averaged across all subjects. CML is the baseline condition with letters; PWR is pseudoword rhyming; RWR is real-word rhyming; and ACR is alternate-case rhyming. The images were acquired by subtracting the baseline control (CML) from the three experimental conditions. The activation shown here has a height threshold of $P = 0.001$ ($z = 3.9$) and a corrected extent threshold of $P = 0.05$. The sagittal, axial and coronal views in the figures are scaled corresponding to the Talairach and Tournoux convention (Talairach and Tournoux, 1988). (d) The common areas (i.e. the cortical regions/voxels that were not significantly different among the three conditions) activated in rhyming words, pseudowords and words printed in alternate-letter case. All slices were 6 mm thick.

We also performed masked conjunction analysis using SPM97 (Price *et al.*, 1997) with a height threshold of $P = 0.001$ (corrected) to assess the common regions for rhyming words, pseudowords and words printed with alternate letter cases. The conjunction results confirmed that all three conditions activated these same brain regions (see Fig. 1d).

Word and pseudoword rhyming also showed consistent activation in the right cerebellum which was strongest for pseudoword rhyming. In addition, rhyming pseudowords activated left supramarginal gyrus, while word rhyming showed significant activation in the left posterior-temporal gyrus around Brodmann areas 21 and 22. However, the activation in the latter two regions was almost solely attributable to female subjects (see Table 3).

The results of these contrasts also showed that even with the highly conservative criteria, pseudoword rhyming activated more voxels in the left posterior prefrontal regions (56% more than RWR and 55% more than ACR), the left inferior temporal-occipital junction (253% more than RWR and 40% more than ACR) and in the right cerebellum (238% more than RWR and 823% more than ACR) (see Fig. 2). Additional contrasts between word and pseudoword rhyming (i.e. PWR-RWR and PWR-ACR) using a less conservative threshold (i.e. a height threshold of $P = 0.001$ [uncorrected]), again, revealed that pseudoword rhyming activated significantly more voxels in these regions. The contrast between rhyming words and words printed in alternate letter case (i.e. RWR-ACR) using the same threshold criteria showed no additional activation. (see Fig. 3 and Table 4)

On average, female subjects' data are very similar to the group data (see Table 3). They showed significant activation in the left

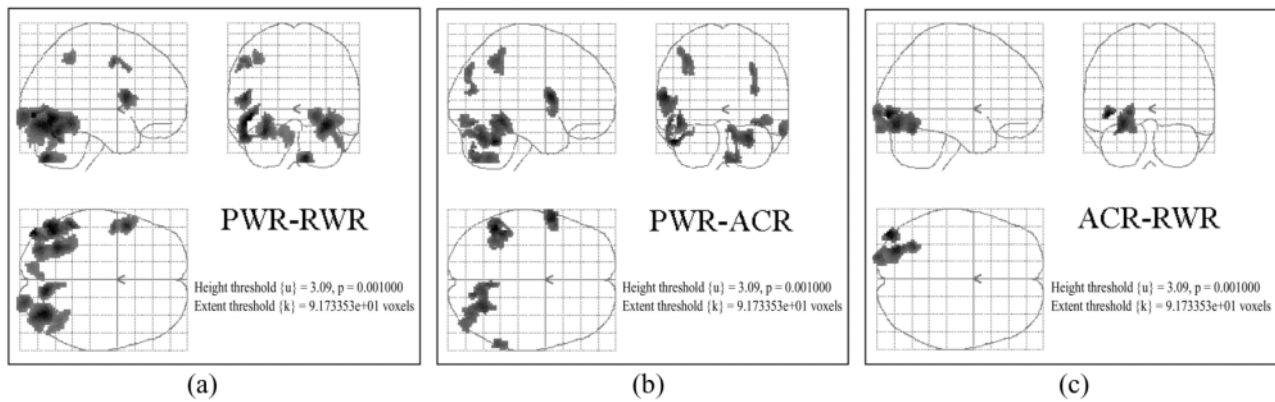


Figure 3. (a,b) Additional activations in rhyming pseudowords relative to rhyming words and words with alternate letter case. (c) Additional activations in rhyming words with alternate-letter case relative to rhyming words printed in normal font types. All activations in the regions shown in (a)–(c) were statistically significant at a height threshold of $P = 0.001$ (uncorrected).

Table 4
Additional activations in brain regions due to rhyming pseudowords and words with alternate letter case relative to rhyming words printed in normal letter case

Regions	Contrasts										
		Hemisphere	PWR–RWR			PWR–ACR			ACR–RWR		
			<i>x y z</i>	Voxels	(Z)	<i>x y z</i>	Voxels	(Z)	<i>x y z</i>	Voxels	(Z)
Cerebellum	L	----			–48 –52 –30	179	(5)	----			
	R	10 –72 –46	209	(5)	26 –64 –26	349	(4.3)	----			
Inferior temporal–occipital junction	L	–46 –66 –10	1523	(5.4)	–44 –44 –10	116	(4.5)	----			
	R	32 –76 –14	1277	(5.2)	34 –76 –14	118	(4.1)	----			
Occipital lobe	L	----			----			–28 –82 –14	657	(4.8)	
	R	----			32 –76 20	93	(3.8)	–42 –88 –6	94	(5.2)	
Posterior-prefrontal cortex	L	–52 10 12	188	(4.8)	–58 6 14	250	(4.6)	----			
	R	–50 –4 46	95	(4.2)							
Supramarginal gyrus	L	–38 –48 50	92	(3.7)	----			----			

Table 4 shows cortical regions significantly activated at a height threshold of $P = 0.001$ and an extent threshold of $P = 0.05$. The coordinates represent peak voxels. PWR–RWR, activation associated with pseudoword rhyming after subtracting the activation due to word rhyming; PWR–ACR, activation associated with pseudoword rhyming after subtracting alternate case rhyming; ACR–RWR, activation associated with alternate case rhyming after subtracting the activation due to word rhyming. L, left; R, right.

posterior-temporal gyri around Brodmann areas 21 and 22 in word rhyming and alternate-case rhyming conditions. Females also showed strong activation in the left cingulate gyrus in all three rhyming conditions relative to the baseline controls. Males did not show significant activation in the cingulate and the left posterior-temporal gyri relative to the baseline controls. However, neither the combined group data nor the males and females analyzed separately showed significant activation in the right hemisphere in rhyming words and pseudowords. Only weak activation was observed in the right occipital region during pseudoword rhyming in males and in the group analysis. Little indication of significant participation of other regions in the right hemisphere was observed even when the statistical threshold was reduced.

Discussion

In this study, we used rhyming judgment tasks with visually presented words and pseudowords to maximize the burden of neural activity on the computation of speech codes. Our baseline control conditions required minimal speech codes and lexical semantics – stimuli were primarily consonant letter strings and non-linguistic symbols. The results of the study suggest that there are highly lateralized epicenters engaged in

the phonological processing of words and pseudowords. These epicenters appear to be in the left hemisphere for both males and females. The latter is inconsistent with some of the recent reports on strong right hemisphere participation in females during phonological processing (Shaywitz, *et al.*, 1995; Pugh *et al.*, 1996). However, because fewer subjects (six male and six female) participated in our study compared to previous ones concerned with gender differences, our results may not be representative of the general population. Further investigation is needed to substantiate previous observations on gender differences in phonological processing (Frost *et al.*, 1999).

In addition to the above results, rhyming words and pseudowords involved common brain regions although activation was stronger and spread to more tissues for pseudowords than for words. The difference in the size of activation cannot be solely attributed to the perceptual familiarity of the stimuli and decoding effort measured by response speed and accuracy, since the online performance data showed no significant difference in either response time or accuracy between the rhyming conditions. In fact, both response speed and accuracy were virtually identical, especially in rhyming pseudowords and words with mixed letter cases even though the latter was more visually distorted and anomalous than the pseudoword stimuli. We believe the differences are likely due to the qualitative

difference between word and pseudoword rhyming processes (discussed further below).

Stronger activation for pseudoword than for word stimuli has been reported in several imaging studies before (Price *et al.*, 1996; Rumsey *et al.*, 1997; Paulesu *et al.*, 2000). Our results are consistent with earlier observations in that tasks involving pseudowords consistently showed stronger activation than those with real words. However, regarding phonological processing, our findings differ from previous reports both in activation patterns and in the extent that cortical regions overlap during the computation of speech codes for words and pseudowords. Specifically, the activation in the left inferior temporal-occipital junction has not been sufficiently demonstrated to be associated with phonological processing (Price *et al.*, 1996; Rumsey *et al.*, 1997). Our results strongly indicate that this region is important in orthography-phonology mapping in addition to 'word form' detection as previous imaging studies suggested (Posner *et al.*, 1989). Previous studies also suggested significant activation in the left middle temporal regions during pseudoword processing (Price *et al.*, 1996; Rumsey *et al.*, 1997) which was not apparent in our results.

The exact causes of these differences are difficult to determine. One possibility is that previous studies did not effectively control for task difficulty and perceptual familiarity when pseudowords were included in imaging paradigms (see discussions earlier in the paper). Therefore, stimulus-specific processing characteristics (i.e. pseudoword effects) in previous studies cannot be effectively separated from other contributing factors such as task difficulty and perceptual familiarity. The results of our study substantiated previous observations by taking into account these factors. Because we used identical tasks (i.e. rhyming) with simple responses (i.e. 'yes' or 'no' rhyming judgment)² for all the critical conditions, and controlled for perceptual familiarity, the differences in activation intensity can be more reliably attributed to the qualitative difference between the functional stimuli (i.e. words versus pseudowords). However, as in any imaging studies of higher brain functions, caution must be exercised in attributing activation differences to functional stimuli. It is possible that the difference in activation patterns between words and pseudowords were partly due to the experimental task (i.e. making rhyming judgments) used in the study. We cannot be certain if the same pattern of activation would be replicated if we had used more natural word and pseudoword reading conditions.

Conjoint and Extended Phonological Epicenters and their Implications for Word and Pseudoword Reading

Current results suggest that although reading words and pseudowords share common brain regions, pseudoword reading may rely on more extended neural systems than word reading. Our results showed that pseudoword rhyming activated the left supramarginal gyrus which did not appear to play a significant role in rhyming words. Pseudoword rhyming also induced greater change than rhyming words in blood volumes (see Table 3) and voxel size around the epicenters of neural activity in the left inferior occipital-temporal junction and the left posterior prefrontal regions. However, it remains unclear whether the enhanced blood volume and activation size were caused by an increased burden on the shared neural system during pseudoword rhyming or by the participation of the more extended neural circuitries needed for processing pseudowords than words. Most likely, both contributed to the size and volumes of activation in pseudoword rhyming (Plaut *et al.*, 1996).

Neuropsychological studies of patients have repeatedly shown that impairment in reading regularly spelled words almost always coincides with a poor ability in reading pseudowords (Fiez and Petersen, 1998; Shallice, 1988). Recent work on this selective impairment emphasizes the computational mechanisms underlying phonological processes (Coltheart *et al.*, 1993; Seidenberg *et al.*, 1994; Plaut *et al.*, 1995, 1996; Van Orden *et al.*, 1997). The results of our study further suggest that computing phonological codes for words and pseudowords may involve slightly different neural networks in addition to shared neural systems. Thus, selective impairment in reading certain classes of words and pseudowords may also result from damage to neural systems adjacent to or surrounding the phonological epicenters. These extended neural systems may be important for building phonological structures for pseudowords and unfamiliar words, but less crucial for reading familiar words. The relation of our rhyming tasks to natural word reading processes, however, must be interpreted with caution.

The topographical difference in neural systems required for reading pseudowords or unfamiliar low-frequency words may be indicative of differences in the mechanisms underlying word and pseudoword reading. One possibility is that both pseudowords and unfamiliar words are read via a nonlexical routine that assembles finer-grained sublexical codes (e.g. letters) into larger phonological units (e.g. phonotactic and syllable structures). However, for words, even with unusual fonts, mapping orthography to lexical (i.e. whole word) phonology may be accomplished automatically through partial decoding and assembling larger sublexical units (e.g. letter cluster or coda and word body). Such automatic processes are likely carried out by highly trained or specialized networks and neural systems (Plaut *et al.*, 1996; Gabrieli *et al.*, 1998). Consequently, rhyming words may require less extended neural circuitry and tissue than rhyming pseudowords.

A slightly different possibility is that while the computation of speech codes for pseudowords relies heavily on fine-grained mapping from orthography to phonology, for words, especially for familiar words, orthography is activated directly to lexical phonology without the need for a phonological assembly process (Coltheart, 1978; Grainger, 1990; Baluch and Besner, 1991; Sebastian-Galles, 1991; Besner and Hildebrandt, 1987; Seidenberg *et al.*, 1994). Current imaging data do not allow us to differentiate the two possibilities because all critical tasks in the study required phonological decoding.

Nevertheless, our data suggest that the assembled and automatic-activation routines share neural epicenters in reading words and pseudowords. Consequently, damage to epicenters of the system may result in impairment for both word and pseudoword reading. However, if the assembling routine requires extended neural systems beyond the shared epicenters, damage to surrounding neural systems would be more likely to impair pseudoword/nonword reading than word reading.

However, the selectivity of the activation in the left supramarginal gyrus for pseudowords but not for words and words printed in alternate-letter case in our study does not reconcile with previous studies (Shallice, 1981; Roeltgen *et al.*, 1983; Petersen *et al.*, 1988, Ojemann *et al.*, 1989; Fiez *et al.*, 1995; Price *et al.*, 1997). Previous studies using neuroimaging, transcranial stimulation and patients with central nervous system lesions reported the participation of the left supramarginal gyrus with real word stimuli in overt naming and other phonological tasks. Given the narrow methods we used in the current study, it is difficult to draw strong conclusions about the region from our

results. The inconsistency between the current and previous results may lie partly in experimental tasks and conditions under which the tasks were performed. In the current study, subjects performed a simple silent rhyming task comparing stimuli between two consecutive trials. Previous studies often required explicit segmentation and comparison of the phonological structure of the stimuli (Fiez *et al.*, 1995; Price *et al.*, 1997) or involved patients with brain lesions and other neuropsychological deficits (Shallice, 1981; Roeltgen *et al.*, 1983; Ojemann *et al.*, 1989). Future studies need to sort out task-specific effects from the general contribution of the left supramarginal gyrus to language-specific operations.

The Role of the Left Inferior Occipital-Temporal Junction in Orthography-Phonology Mapping

A number of studies using neuroimaging and electrophysiological measures (e.g. event-related potential) reported activation in the left inferior occipital-temporal junction (LOTJ) in response to word-like orthographic forms but not to consonant strings or familiar faces (Petersen *et al.*, 1989, 1990; Nobre *et al.*, 1994). Thus, LOTJ has been referred to as 'visual word form areas' (Petersen *et al.*, 1988; Posner *et al.*, 1999). The results of our study are consistent with these observations. Our word and pseudoword rhyming conditions revealed strong activation in the LOTJ areas in comparison to the control conditions in which subjects performed visual feature search tasks with either unpronounceable letter strings or nonlinguistic symbols.

Our activation data further suggest that the LOTJ may play a more active role in mapping orthographic form to phonological codes than simply detecting orthographic forms. Our results showed that the size and strength of activation in the LOTJ regions including the left fusiform gyrus increased from rhyming words to rhyming pseudowords (Fig. 3). Although words presented in the alternate letter case condition were orthographically unconventional, the size of activation in the LOTJ region was significantly smaller with alternate case than with pseudowords. These data suggest that the strong activity in this region with pseudoword rhyming could not be simply attributed to orthographic form detection. Instead, LOTJ may be engaged in verification and mapping orthographic form to sublexical phonological codes as a result of phonological assembly processes. As discussed earlier, words, even when printed in unconventional orthography, may activate lexical phonology after partial encoding of sublexical codes.

The Role of the Left Posterior Prefrontal Cortex in Phonological Processing

Neuroimaging data concerning the role of the left posterior prefrontal cortex have been inconsistent. Several studies showed the participation of the left prefrontal cortex in phonological processing (Petersen and Fiez, 1993; Zatorre *et al.*, 1996; Shaywitz *et al.*, 1995; Gabrieli *et al.*, 1998; Paulesu *et al.*, 2000). Others suggest that phonological processes recruit mainly posterior brain regions including the temporal and parietal lobes (Demonet *et al.*, 1992; Small *et al.*, 1996; Price *et al.*, 1997). In addition, the left posterior prefrontal regions (i.e. Brodmann areas 9, 6, 44, 45) and more anterior frontal regions (e.g. Brodmann areas 10 and 47) have often been associated with working memory and semantic processes (Petersen *et al.*, 1988; Posner *et al.*, 1988; Kapur *et al.*, 1994; Raichle *et al.*, 1994; Demb *et al.*, 1995; Buckner, 1996; Gabrieli *et al.*, 1996; Price *et al.*, 1996; Wagner *et al.*, 1998). Our results underscore the

importance of the left posterior prefrontal regions in phonological processing (henceforth, the phonological processing hypothesis) in addition to posterior regions.

As discussed earlier in the paper, the inconsistency of neuroimaging results across studies and laboratories may be due to differences in the sensitivity of imaging techniques (e.g. high-versus low-resolution scanners, scan sequence and statistical power) and variations in experimental paradigms. More importantly, assumptions at the core of research hypotheses and experimental designs often affect the interpretation of brain activation and its relation to cognitive functions. For example, the interpretation of imaging data about the functional anatomy of the prefrontal cortex is highly constrained by our assumptions about the way in which cognitive functions may be fractionated into component processes (Shallice, 1988; Van Orden, and Paap, 1997). While keeping this caveat in mind, we believe that the seemingly inconsistent observations between our results and some of the previous findings actually suggest important cognitive operations common to tasks used in many of the studies, especially those showing the participation of the left posterior prefrontal regions.

The effect of phonological processing was implicit in many previous studies. Several brain imaging studies on working memory, verbal or nonverbal, reported activation in the left posterior prefrontal regions only when the control conditions (e.g. rest, visual fixation or visual feature search) required little phonological processing (Wagner *et al.*, 1998; Kapur *et al.*, 1994; Buckner *et al.*, 1996; Courtney *et al.*, 1996, 1998; Gabrieli *et al.*, 1996; Cohen *et al.*, 1997). However, when a baseline condition did call for phonological processing as the word repetition condition in Buckner *et al.* (Buckner *et al.*, 1996), the activation in these regions was diminished after subtracting out the baseline activation.

The phonological processing hypothesis we propose here is consistent with previous findings that the left posterior prefrontal regions were activated when tasks required the retrieval of verbal information or analytic processes (Buckner, 1996; Gabrieli *et al.*, 1996; Courtney *et al.*, 1998; Ungerleider *et al.*, 1998). Retrieving verbal information and conducting high-level reasoning processes would certainly incur phonological representation. These processes are in contrast to visual working memory demands which often did not activate these regions on the left when tasks minimized the effects of phonological processing (Grady *et al.*, 1994; Haxby *et al.*, 1994; Courtney *et al.*, 1996).

The phonological processing hypothesis is further supported by evidence showing that the left posterior prefrontal cortex was recruited even when experimental tasks did not require verbal semantic retrieval (Buckner *et al.*, 1996; Cohen *et al.*, 1997; Courtney *et al.*, 1998). Our data again showed significantly more activation in the left posterior prefrontal regions for rhyming pseudowords than rhyming real words. Since our rhyming tasks emphasized the computation of speech codes, and word and pseudoword stimuli were presented separately in blocks of trials at a rapid rate (1/s), active semantic processing would be more likely amplified for words than pseudowords, which, by definition, have no meaning. However, this is not the case. Instead, pseudoword rhyming showed more extensive activation in these regions than word rhyming. On the other hand, tasks involving explicit semantic retrieval tend to show activation in more anterior regions of the left prefrontal cortex such as Brodmann areas 10, 46 and 47 (Petersen *et al.*, 1988; Raichle *et al.*, 1994; Buckner, 1996). The involvement of these brain

regions was not apparent in our study which did not require active semantic processes.

Therefore, previous findings and the current results taken together indicate that the left posterior prefrontal region is crucial for tasks that call for phonological processes in addition to other cognitive functions (Gabrieli *et al.*, 1998). However, it is unclear whether this region is engaged primarily in maintaining the output of phonological codes or is an essential part of the neural network for mapping orthography to phonological codes.

The phonological processing hypothesis is by no means meant to diminish the possibility that both semantic and phonological processes call for the participation of the left posterior prefrontal regions. Since semantic processing is likely to be automatically coupled with or dependent upon phonological processes in reading (Van Orden and Goldinger, 1994; Van Orden *et al.*, 1997; Xu, 1998), it may be difficult to clearly separate the two processes and their functional anatomy. What can be clarified in future research with neuroimaging techniques is, perhaps, the relative contribution of the left prefrontal regions to important language systems.

It is important to point out that although making rhyming judgments (e.g. cite-night) differs significantly from traditional memory tasks (e.g. the *n*-back task in which responses can often be made on the basis of stored visual features), rhyming judgments require active participation of working memory (i.e. holding in mind the speech codes/phonological structure of the preceding word or nonword). Even though the effect of memory load in the rhyming tasks should be reduced after subtracting out the baseline activation, the extent to which our results represent phonological processing and not general working memory operation cannot be determined with our study design. It would be misleading to suggest that the left posterior-prefrontal region does not play a role in working memory since phonological processing is considered an important part of working memory (Baddley, 1986, 1992).

Conclusion

The results of our study suggest that in addition to the shared neural epicenters for phonological processes, the computation of phonological codes for pseudowords and, perhaps, for unfamiliar low-frequency words, require a much larger neural network than that engaged in reading words. An extended and complex neural system for reading pseudowords, revealed through this study of normal brain functions, provides evidence for understanding the neural basis of selective impairment of reading dysfunctions after a brain lesion. It also lends support to the possibility that form-function mapping for words and pseudowords invokes slightly different mechanisms. One interpretation is that, for pseudowords, form-phonology mapping may require assembling finer grained sublexical codes (e.g. at the letter level); for words, such mapping may be accomplished with partial activation of much larger functional units (e.g. clusters of letters). However, the current results do not allow us to distinguish whether an extended neural network is needed to maintain coherent activation of phonological codes for unfamiliar letter strings or for participating in the initial recoding processes prior to a coherent phonological representation.

In addition, task characteristics (e.g. emphasizing phonological judgments) also limit our ability to draw broad conclusions on the contribution of the observed brain regions in natural reading conditions. Baseline conditions are also key to the activation patterns observed in the rhyming conditions.

Previous imaging studies often used 'rest' or 'a fixation point' as baseline controls. We chose 'active' tasks as controls to take into account the effect due to non-language-specific perceptual features, decision responses and working memory load associated with the rhyming tasks. However, no matter how careful we are to construct an appropriate baseline, it would be rare that a cognitive task would only differ from another task by one processing component of interest, in this case, phonology (Van Orden and Paap, 1997). It is possible that the pattern of our results were sculpted to some extent by our baseline controls. Future studies must take task characteristics into consideration in the search for neural networks of language.

Notes

1. Price *et al.* (Price *et al.*, 1996b) reported results of a PET study which showed more brain regions were involved in lexical decision tasks when stimuli were presented for 150 ms at a rate of 1.5 s/stimulus than when they were presented at a longer duration (~1000 ms at a rate of 1 s/stimulus). Behavioral studies have demonstrated that the ease of lexical judgments depends on the characteristics of words and nonwords in an experimental list, including word frequency and nonword lexicality (Stone and Van Orden, 1993; Lupker *et al.*, 1997). Unfortunately, word frequency and nonword lexicality were not reported in the study. However, based on the authors's description, the nonwords seemed largely to be pronounceable pseudowords that looked very much like real words. If that is the case, the lexical decision tasks could be fairly difficult. Therefore, it is possible that the 150 ms presentation duration was too short and the tasks were too difficult for the subjects. Consequently, subjects might have developed various cognitive strategies to cope with the tasks. These strategies may involve cognitive systems that are not crucial for normal word reading and lexical decision. In contrast, in the condition with long presentation duration, stimulus viewing opportunity was sufficient, and therefore cognitive strategies were minimized. Since the authors did not report performance data, the effects of stimulus duration in the study can not be further evaluated.
2. Rhyming judgment with 'yes' or 'no' effectively minimized performance differences between words and pseudowords. This is in contrast to naming or lexical decision tasks which often maximize behavioral differences as a consequence of processing the two qualitatively different stimuli – words versus pseudowords.

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