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Manipulation of Length and Lexicality Localizes the Functional Neuroanatomy of Phonological Processing in Adult Readers

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Abstract

■ In a previous study of single word reading, regions in the left supramarginal gyrus and left angular gyrus showed positive BOLD activity in children but significantly less activity in adults for high-frequency words [Church, J. A., Coalson, R. S., Lugar, H. M., Petersen, S. E., & Schlaggar, B. L. A developmental fMRI study of reading and repetition reveals changes in phonological and visual mechanisms over age. *Cerebral Cortex, 18,* 2054–2065, 2008]. This developmental decrease may reflect decreased reliance on phonological processing for familiar stimuli in adults. Therefore, in the present study, variables thought to influence phonological demand (string length and lexicality) were manipulated. Length and lexicality effects in the brain were explored using both ROI and whole-brain approaches. In the ROI analysis, the supramarginal and angular regions from the previous study were applied to this study. The supramarginal region showed a significant positive effect of length, consistent with a role in phonological processing, whereas the angular region showed only negative deflections from baseline with a strong effect of lexicality and other weaker effects. At the whole-brain level, varying effects of length and lexicality and their interactions were observed in 85 regions throughout the brain. The application of hierarchical clustering analysis to the BOLD time course data derived from these regions revealed seven clusters, with potentially revealing anatomical locations. Of note, a left angular gyrus region was the sole constituent of one cluster. Taken together, these findings in adult readers (1) provide support for a widespread set of brain regions affected by lexical variables, (2) corroborate a role for phonological processing in the left supramarginal gyrus, and (3) do not support a strong role for phonological processing in the left angular gyrus. ■

INTRODUCTION

Regions near the left temporo-parietal junction, including the supramarginal gyrus (Figure 1A) and the angular gyrus (Figure 1B), have been suggested to form part of a phonology-mediated pathway for decoding visual words (for a review, see Schlaggar & McCandliss, 2007). Evidence for this concept has come from lesion, behavioral, and neuroimaging research (Frost et al., 2009; Palmer, Brown, Petersen, & Schlaggar, 2004; Jobard, Crivello, & Tzourio-Mazoyer, 2003; McDermott, Petersen, Watson, & Ojemann, 2003; Pugh et al., 2001; Fiez & Petersen, 1998; Geschwind, 1965).

In addition, there is evidence of a divergence in function between the angular and the supramarginal gyrus from a number of studies, with the angular gyrus proposed to have a larger role in lexical or semantic processing (e.g., Binder, Desai, Graves, & Conant, 2009; Graves, Desai, Humphries, Seidenberg, & Binder, 2009; Price, 2000; Binder et al., 1999). In parallel, there is strong evidence for the angular gyrus as part of the "default mode network," showing negative BOLD activity during tasks (Raichle, 2006; Raichle et al., 2001; Shulman et al., 1997), whereas the supramarginal gyrus has consistently shown positive BOLD activity (e.g., Graves et al., 2009; Binder, Medler, Desai, Conant, & Liebenthal, 2005).

The study described here set out to further explore, in adults, a difference previously found between children and adults (Church, Coalson, Lugar, Petersen, & Schlaggar, 2008). In brief, in a previous fMRI study, we compared 25 children ages 7–10 years and 25 adults ages 18–32 years reading aloud visually presented high-frequency words. The results indicated that adults had significantly less BOLD activity than children in regions of the left supramarginal and angular gyri, even when the subject groups were matched for reaction time and accuracy (Figure 1). There were differences, however, in the adult time course profiles of the two regions. The supramarginal region was active in adults but significantly less so than in children. In contrast, the angular region, active in children, was not significantly active in adults (compare adult time courses for high-frequency word reading in Figure 1A and B). However, the similar activity observed in children for high-frequency word reading in these two regions was interpreted as evidence for similar processing roles—putatively phonological processing—in development.

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Figure 1. Three ROIs from a developmental study of high-frequency word reading (Church et al., 2008). Children ages 7–9 years ($n = 25$) and adults ages 18–32 years ($n = 25$) performed high-frequency word reading aloud. Region A, in the supramarginal gyrus ($-52, -42, +24$), shows greater activity for children than adults reading high-frequency single words. For the same tasks, Region B, in the angular gyrus ($-49, -62, +29$), shows significant activity only in children. Region C, in the left extrastriate cortex ($-38, -60, -12$), had significantly less activity for adults than children. Figure adapted from Figure 4 in Church et al. (2008). The surface-rendered image was created using CARET software and surface-based atlases (Van Essen & Dierker, 2007; Van Essen, 2002; Van Essen et al., 2001).
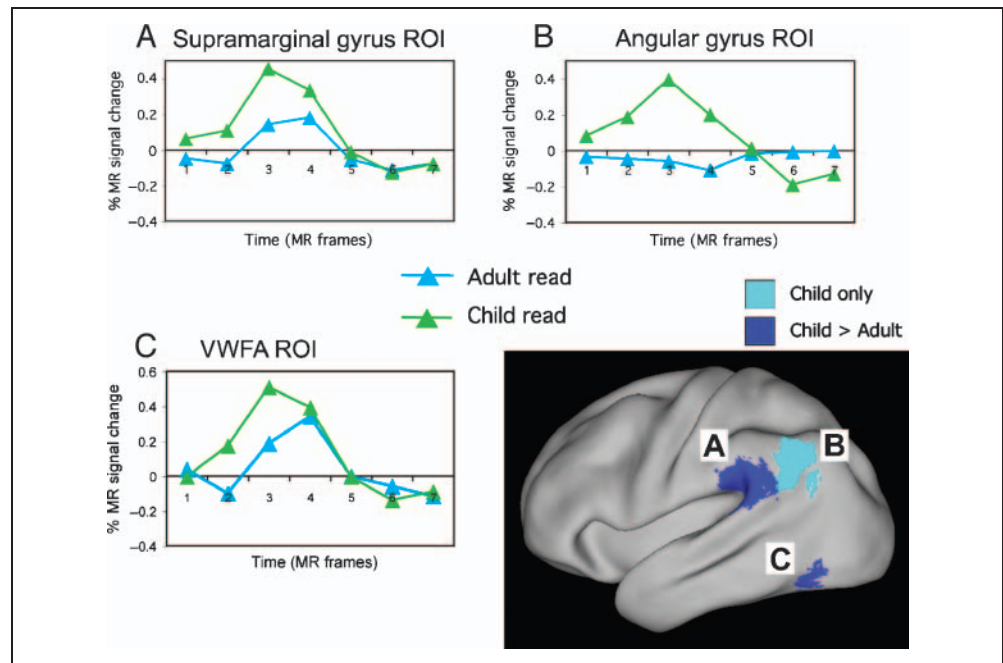
Interestingly, other studies have shown that readers with dyslexia demonstrate altered developmental effects, with decreased activity in the temporo-parietal regions compared with age-equivalent fluent readers, which has been interpreted as a disruption in phonological processing that may contribute to their dyslexia (Hoeft et al., 2006; Kronbichler et al., 2006; Shaywitz et al., 2002; Eden & Zeffiro, 1998; Horwitz, Rumsey, & Donohue, 1998). A recent meta-analysis of studies of dyslexia reports that a region in the left supramarginal gyrus was consistently shown to be less active in dyslexics than controls (Richlan, Kronbichler, & Wimmer, 2009).

Pugh et al. (2001) have proposed that phonological strategies for word reading in temporo-parietal regions develop early and serve to "train" other ventrally located regions. This later developing ventral processing stream involves regions in extrastriate cortex, possibly including the purported visual word form area (VWFA), to support mature fluent reading (discussed further below, McCandliss, Cohen, & Dehaene, 2003; Cohen et al., 2002; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002; Pugh et al., 2001).

In total, these studies and our previous developmental study suggest that phonological processing demands are necessarily high for early readers but decrease with increasing age and reading skill. One interpretation of this decreased phonological demand in adults is that it would then lead to decreased activation of the putative phonological processing regions, namely, in the supramarginal and angular gyri.

We wished to explore this proposition further in adults by testing to see if adult activity in these putative phonological regions could be increased with more phonologically demanding stimuli (i.e., could we get adults to have childlike levels of activity using phonological manipulations?). An important issue was whether the developmental changes observed previously stem from a general decrease in reliance on phonological processes across development during reading or whether the developmental changes may simply reflect the adults' high level of familiarity with these specific stimuli (high-frequency words). Specifically, the phonological demands of high-frequency words and thus the BOLD activity in supramarginal and angular regions could be reduced in mature, fluent readers because of the relative fluency and familiarity of adults for the processing of these words as compared with children. If this item-specific hypothesis is correct, then stimulus items that produce higher phonological demands should drive more phonological processing in adults and be reflected by greater activity in the supramarginal and angular gyrus regions.

Length and lexicality of stimuli are widely thought to affect phonological demand in studies of reading (Rastle & Coltheart, 2006; Harm & Seidenberg, 1999, 2004; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Rastle & Coltheart, 1998; Weekes, 1997; Coltheart, Curtis, Atkins, & Haller, 1993). Length effects are thought to be an important index of phonological processing because of the proposed serial nature of the "assembled" or "sublexical" route in the dual-route cascade models (Rastle & Coltheart, 2006; Coltheart et al., 2001). Similarly, parallel distributed processing models of reading also have a phonological component that is impacted by length and has greater emphasis in the training of the model than an orthographic component, mirroring what is seen in human development

(Harm & Seidenberg, 2004; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989; McClelland & Rumelhart, 1981). The lexicality of a stimulus, although not affecting a phonological processor per se, affects the success of other processes brought to bear on word reading (namely elements of semantic and orthographic processing).

Length and lexicality have been shown to interact behaviorally, such that length affects reaction time more for less familiar items (Weekes, 1997), suggesting less holistic processing of unfamiliar items. The present article explores the effects of length and lexicality on the level and pattern of differential activity in the two purported phonological regions in the angular and supramarginal gyrus as well as a purported lexical region, the VWFA, in healthy literate adults.

The purported VWFA is part of a proposed posterior ventral neural processing pathway thought to be important for fluent reading. The dual-route cascade model of word reading, although not brain based, proposes that in addition to an "assembled route" of orthographic-to-phonological conversion, there is a pathway of visual word processing involving a visual word lexicon that operates in parallel (Coltheart et al., 2001). Particular attention has been paid to the purported VWFA located in the left hemisphere at approximately $x = -43$, $y = -54$, $z = -12$, Talairach coordinates (Cohen & Dehaene, 2004). The VWFA has been shown to have greater activity for words than consonant strings or nonwords (reviewed by McCandliss et al., 2003). However, this region has also shown decreased activity for words compared with pseudohomophones (Bruno, Zumberge, Manis, Lu, & Goldman, 2008; Kronbichler et al., 2007) or case deviants (Kronbichler et al., 2009) or pronounceable nonwords (Bruno et al., 2008; Kronbichler et al., 2004, 2007; Mechelli, Gorno-Tempini, & Price, 2003). In a study published in 2009, Van Der Mark et al. (2009) found that dyslexic children fail to show a difference in activity in occipito-temporal cortex between false fonts and words that is observed in unaffected children. In our developmental study, a region near the VWFA showed stronger activity in children than adults for high-frequency word reading, just as the more dorsal supramarginal and angular gyrus regions did (Church et al., 2008). We hypothesized that the VWFA region would be less likely to be sensitive to length effects because of the parallel processing proposed to occur within the orthographic processing aspects of the two main reading models. We also predicted that we would see an effect of lexicality (nonwords greater than words) in this region because of adults' lack of prior experience with our nonword stimuli. We anticipated relatively increased activity for nonword than for word stimuli owing to the relatively greater processing demands for nonwords in the region.

In addition to these regional explorations, the current study examined whole-brain effects of length and lexicality stimulus manipulations. Previous research manipulating stimulus features led us to expect a large number of active regions for each manipulation, with potential for overlapping effects (Graves et al., 2009; Binder et al., 2005; Mechelli et al., 2003; Mechelli, Friston, & Price, 2000). For the whole-brain results, therefore, we looked for a method to characterize brain regions beyond statistical thresholds. When dealing with large numbers of regions, each with varying task effects, data clustering tools can reveal patterns that are difficult to detect by standard analyses. Thus, the data described here were examined using hierarchical clustering algorithms of concatenated time courses across conditions to identify sets of regions with similar activation profiles (Ploran, Nelson, Velanova, Petersen, & Wheeler, 2007; Salvador et al., 2005; Cordes, Haughton, Carew, Arfanakis, & Maravilla, 2002).

METHODS

Participants

A total of 26 adults participated in this experiment. Data from two subjects were removed from the analysis; one was removed for experimental errors during acquisition and the other for aberrant performance and excessive movement. The remaining 24 participants were right-handed adults (12 women, 21–30 years old, average 25 years). All participants gave informed consent. Participants were college, graduate or medical students, or college graduates, and most were from the Washington University community. All subjects were screened for neurological, psychiatric, and/or psychological diagnoses by telephone interview and questionnaire.

The Washington University Human Studies Committee approved the study, and all participants were reimbursed for their participation.

MRI Data Acquisition and Preprocessing

A Siemens 1.5-T MAGNETOM Vision system (Erlangen, Germany) was used to collect the anatomical and functional MRI data. Structural images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time [TR] = 9.7 msec, echo time = four msec, flip angle = 12°, inversion time = 300 msec, voxel size = 1.25 × 1 × 1 mm). An asymmetric spin-echo echo-planar pulse sequence was used to collect functional data (TR = 2.18 sec with a 904-msec delay, total TR = 3.08 sec, T2* evolution time = 50 msec, flip angle = 90). Complete brain coverage was achieved during each scan by obtaining 73 frames of 16 contiguous interleaved 8-mm axial slices (3.75 × 3.75 mm in-plane resolution). The brief delay after each TR was added to each frame to minimize scanner noise and to allow subject task responses to be more easily monitored. Steady state was assumed starting with the fourth frame.

Task and Experimental Design

A 2 × 2 experimental design varied lexicality in two levels (low-frequency words and pronounceable nonwords)

and length in two levels (one-syllable four- to six-letter items and three-syllable seven- to nine-letter items). Frequency was not significantly different between the one- and the three-syllable low-frequency words ($p = .9$ by two-tailed t test). Other word parameters were not controlled for in the stimulus design, and as expected (see Balota, Cortese, Sergent-Marshall, Spieler, & Yap, 2004), orthographic neighborhood and summed bigram frequency were highly correlated with length of the stimuli, as measured by number of letters ($r = -.71$ and .84, respectively, $p < .0001$, see Supplemental information). The mean bigram frequency of the stimuli was less correlated with stimulus length ($r = .39$) and thus was used as a regressor in post hoc testing of the functional data (see Supplemental information). High-frequency words, the same as those reported in Church et al. (2008), were also presented to replicate the effects observed for those stimuli in adults (one-syllable two- to seven-letter words). This high-frequency word condition was not included in the analyses of length or lexical familiarity because stimulus length and other factors were not matched to the new low-frequency and nonword stimuli. It was anticipated that the high-frequency word condition would provide a reference point to the previous study with which to compare the 2×2 length $\times$ lexicality manipulation. Stimuli were designed using the English Lexicon Project at Washington University (Balota et al., 2007). Examples of the stimuli and details regarding their length and frequency are summarized in Table 1.

Headphones dampened scanner noise and enabled communication with participants. A Power Macintosh computer (Apple, Cupertino, CA) equipped with PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993) was used for display of visual stimuli. An LCD projector (Sharp model PG-C20XU) was used to project stimuli onto an MRI-compatible rear-projection screen (CinePlex) at the head of the bore, which the participants viewed through a mirror attached to the coil.

In all five conditions, participants viewed a white fixation cross on a black background. The fixation was always onscreen, except when replaced by a single word or non-

word stimulus, with each letter subtending 0.5° of horizontal visual angle. Stimulus duration was 950 msec. In each run, 21 stimuli were presented every second, third, or fourth MR frame (TR = 3.08 sec; average interstimulus interval 9.24 sec) in a pseudorandom fashion. This jittering allowed the event-related time course of the response to be extracted (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). For each condition, participants were asked to read aloud the stimulus as quickly, clearly, and accurately as possible. Participants performed 15 total experimental runs with 21 stimuli each, and each participant saw a total of 63 trials of each condition. Only one condition type was presented during each experimental run.

Multiple researchers have addressed the possibility of artifacts from scanning during overt verbal responses in the MRI environment (Mehta, Grabowski, Razavi, Eaton, & Bolinger, 2006; Palmer et al., 2001; Birn, Bandettini, Cox, & Shaker, 1999). These articles demonstrated that acquisition of interpretable, relatively artifact-free images of tasks during overt verbal responses was possible and that the regions most affected by speech were basal areas of the brain and brain regions around CSF (Mehta et al., 2006). Also, other studies of reading-related tasks have not observed significant speaking-related artifacts (Church et al., 2008; Fair, Brown, Petersen, & Schlaggar, 2006; Binder et al., 2005; Brown et al., 2005; Schlaggar et al., 2002). Participants were encouraged to minimize movements throughout the scan, including movements during their vocal responses. To enhance participants' abilities to remain still, we applied a thermoplastic mask that molds to an individual's face and attaches to the head coil.

Behavioral Measures

Behavioral data were collected with digital voice recording software for later analysis as described by Nelles et al. (2003). In brief, because scanner noise obscures the digital recordings, each run of each participant was processed with in-house software that uses adaptive spectral subtraction to

Table 1. Characteristics of Stimuli

Condition	Example Stimuli	Average Length in Letters (Range)	Average Frequency (HAL)	Average % Correct	Average RT (msec)
High-frequency words, one syllable	few; street	4.33 (2–7)	375127	99.735	599.792
Low-frequency words, one syllable	lank; prawn	4.28 (3–5)	104.5	99.140	662.309
Low-frequency words, three syllables	jocular; pastrami	8 (7–9)	107.3	99.206	701.587
Nonwords, one syllable	flum; blosp	4.28 (3–5)	N/A	99.405	683.558
Nonwords, three syllables	doricor; giltondo	8 (7–9)	N/A	98.544	900.461

separate the scanner noise from vocal responses (Nelles et al., 2003). Response times were calculated as the length of time from the onset of stimulus presentation until the start of the vocal response to that stimulus. Response time and accuracy (i.e., % correct) were computed for each individual for each run.

fMRI Processing and Data Analysis

General Features

Preliminary image processing was carried out to reduce noise and artifacts (for detailed procedures, see Miezin et al., 2000). Preprocessing included removal of a single pixel spike caused by signal offset, correction for subject movement within and across runs, and slice-by-slice normalization to correct for changes in signal intensity because of acquisition of interleaved slices.

Participant motion was corrected and quantified using an analysis of head position on the basis of rigid body translation and rotation. The data derived from adjustments needed to realign head movement on a frame-by-frame basis were calculated as root mean square (RMS) variance values for translation and rotation in the x, y, and z planes in millimeters. The criterion for removing a scan from analysis was set at total movement of more than 1.5 mm RMS variance. No runs in this study met this criterion; thus, none were discarded.

Data for all subjects were resampled isotropically at $2 \times 2 \times 2$ mm and were transformed into the same standard stereotactic space (Washington University 711-2B space, based on Talairach & Tournoux, 1988). The transformation was done by using an atlas-representative target composed of a mutually coregistered independent sample of 12 healthy adults, which was made to conform to the Talairach atlas using a spatial normalization method (Lancaster et al., 1995). Stereotactic registration was accomplished by 12-parameter affine warping of each individual MP-RAGE image to the atlas-representative target using difference image variance minimization as the objective function. The atlas-transformed image for each participant was checked against a reference average to ensure appropriate registration.

Statistical analyses of event-related fMRI data were based on the general linear model as previously described (Brown et al., 2005; Schlaggar et al., 2002; Miezin et al., 2000), conducted using in-house software programmed in the Interactive Data Language (ITT Visual Information Solutions, Boulder, CO) and C (Ollinger, Shulman, & Corbetta, 2001; Miezin et al., 2000). The general linear model design for each participant included time as a seven-level factor, made up of the seven MR frames (~22 sec, 3.08 sec per frame) after presentation of the stimulus. No assumptions were made regarding the shape of the hemodynamic response function. Each stimulus type was coded separately, leading to five conditions. All analyses included only activity corresponding to correct trials; errors were coded separately and not examined in this report. The effects of reaction time and bigram frequency of the stimuli were examined by separately coding these effects as regressors.

ROI Analyses

An ROI analysis was also performed on three left hemisphere regions in supramaginal, angular, and fusiform gyri, which were derived from the previously reported developmental study (Church et al., 2008) but whose locations were similar to regions described in prior studies of reading (e.g., Binder et al., 2005; Palmer et al., 2004; Cohen et al., 2002). In brief, the supramarginal ROI (located in the left supramarginal gyrus and centered on Talairach coordinates -52, -42, $+24$; 433 voxels, 3.46 cm^3) was extracted from the Monte Carlo–corrected (z score greater than 3.5, $p < .001$, minimum 24 contiguous voxels) image of the main effect of time from that analysis, whereas the angular ROI (located in the left angular gyrus and centered on Talairach coordinates -49, -62, $+29$; 167 voxels, 1.34 cm^3) was extracted from the Monte Carlo–corrected image of the time by age image from that analysis. A region close to the putative VWFA reported in the literature (-43, -54, -12; Cohen & Dehaene, 2004) located in left ventral occipital cortex (centered on Talairach coordinates -38, -60, -12; 95 voxels, 0.76 cm^3) was extracted from the Monte Carlo–corrected Time $\times$ Age image in the previous developmental analysis. In the previous developmental study, all three regions showed a significant effect of Time $\times$ Age (z score > 2.5, $p < .012$), with significantly greater activity in children than adults (Church et al., 2008). All analyses involving these regions also used Box's sphericity correction, adjusting for temporal correlation and possible inhomogeneity of variance over time (McAvoy, Ollinger, & Buckner, 2001; Box, 1954).

Whole-brain Analysis

A 2×2 (Length $\times$ Lexicality) voxel-by-voxel ANOVA was created to extract the main effects of time (across seven MR frames) as well as interaction effects of Length $\times$ Time, Lexicality $\times$ Time, and a three-way interaction of Length $\times$ Lexicality $\times$ Time. All images were smoothed with a two-voxel FWHM smoothing kernel and Monte Carlo corrected at a minimum z score of 3.5 with at least 24 contiguous voxels.

The main effect of time image (an image of significant activity—i.e., not flat BOLD activity—across conditions) was highly reliable and resulted in a large number of regions. Thus, to prioritize the most reliable regions, we thresholded the image at a z score of 9.0 ($p < .00001$) with a minimum region size of 24 contiguous voxels to better separate discrete peaks of interest. Eighty-six regions were extracted from this image with a 4-mm smoothing kernel using in-house peak finding software written by Abraham Snyder. The interaction images of Length $\times$ Time, Lexicality $\times$ Time, and Length $\times$ Lexicality $\times$ Time revealed activation across a substantial volume of the brain. A threshold for each image was chosen that resulted in a similar

number of regions as derived from the main effect of time image (i.e., 86 regions). The Length × Time image was thresholded at a z score of 5 ($p < .00001$), resulting in 77 regions. The Lexicality × Time image was thresholded at a z score of 4 ($p < .0001$), resulting in 71 regions. The Length × Lexicality × Time image was not as reliable and thus was thresholded at a Monte Carlo–corrected z score of 3.5, with a minimum of 24 voxels (uncorrected, $p < .001$, corrected $p < .05$), which resulted in 33 regions.

The regions extracted from these four images appeared highly overlapping. To remove regions in an unbiased way, we sought a strategy to remove overlaps simultaneously, avoiding the need to prioritize one particular image over another. Thus, each of the four region images was made into a mask, and the four masks were summed. New regions were extracted from that summed image, using the same region software described previously, thus removing multiple instances of the same region. When regions overlapped, the center coordinate of the final region was placed at the highest sum of the masks, thus making it unique to the summed image and slightly dissimilar to the images of its origin. Regions located in white matter or ventricles were removed from the total, resulting in a final set of 85 regions for further investigation (Table 2).

Statistics and time courses were extracted for all of these effects from each region, although these regional effects should be considered merely descriptive. As described above, the coordinates became slightly different from the images of origin in the summed mask process, but they did originate from statistically defined regions. Reported in this descriptive analysis are statistical thresholds lower than those used to originally define the regions. This lower threshold often resulted in a greater number of regions with a statistical effect of length than just those from the Length × Time interaction image (i.e., statistics are reported at a threshold of z score of 2.5, $p < .0124$), whereas the original images were thresholded higher for their particular effect. The lower threshold was used to emphasize the highly overlapping nature of the results and to more fully characterize the final, smaller region set. Box's (1954) sphericity correction was used to adjust for temporal correlation and possible inhomogeneity of variance over time (McAvoy et al., 2001). Effects were considered confirmatory if they had a sphericity-corrected z score greater than 2.5 ($p < .0124$). The separate high-frequency word condition was applied to all of the regions and evaluated for a main effect of time only (z score greater than 2.5). Nearly all of the regions exhibited a number of effects above that threshold (see Table 2). The effect of reaction time was assessed by using response time to each trial for each individual as a single regressor for each time point across all conditions. On an individual subject basis, the reaction times were normalized by subtracting the mean and dividing by the standard deviation. The influence of the mean bigram frequency of each stimulus was also examined as a regressor in the same way as was done for reaction times.

Hierarchical clustering was employed to see if regions segregated into groups on the basis of their profile of time courses for the five conditions (high-frequency words, one- and three-syllable low-frequency words and one- and three-syllable nonwords; Ploran et al., 2007; Salvador et al., 2005; Cordes et al., 2002). Matlab 7.2 toolbox scripts were employed to perform unweighted pair group method with arithmetic mean (or average linkage method) hierarchical clustering on the correlations between the concatenated time courses for each of the regions (The MathWorks, Natick, MA; Handl, Knowles, & Kell, 2005). The correlations between regions were converted to a distance metric of $1 - r$, and a threshold of 0.1 ($r = .9$) was used to report the number of clusters (n.b., the entire clustering tree is shown in Figure 4). Cophenetic r, a measure of how faithfully the cluster tree represents the dissimilarities among the observations, was used as a goodness of fit measure. The cophenetic r should be close to the value 1 (The MathWorks). The average time courses from the resulting clusters of regions were created by collapsing across the regions within each cluster, and the anatomical locations of the region clusters were studied. SPSS 16 was used to determine whether there were reliable differences between the two clusters with the largest number of regions (using cluster as a between–group factor and the time courses for the individual regions within each cluster as the independent observations; SPSS Inc., Chicago, IL). Individual regions within each cluster were also examined for any consistent statistical effects. The same hierarchical clustering approach was employed for the time courses after reaction time was coded as a regressor and separately after the mean bigram frequency was coded as a regressor (see Supplementary information).

RESULTS

Average performance on all conditions was greater than 98%. Reaction time for correct trials and accuracy for the five stimulus types are presented in Table 1. The three-syllable nonword stimuli resulted in significantly longer reaction times than any of the other four conditions ($p < .0001$). The high-frequency one-syllable word stimuli were, on the other hand, read aloud faster than any of the other four conditions ($p < .05$). Movement for all participants was less than 0.71 RMS variance for any single run, and thus no runs were removed from analysis. Average movement overall was 0.25 RMS variance (range = 0.0899–0.705 mm).

ROI Analyses

ROI effects were considered significant if they surpassed a sphericity-corrected threshold of a z score of 2.5 ($p < .0124$). The supramarginal ROI applied from Church et al. (2008) showed a significant effect of Length × Time ($z = 6.01$, $p < .00001$), such that the three-syllable stimuli resulted in significantly greater BOLD activity in adults than the one-syllable stimuli. The high-frequency word

Table 2. The 85 Regions Used in the Whole-brain Analysis

X	Y	Z	Voxels		Brodmann's area	Time sph z	Length × Time sph z	Lexicality × Time sph z	Length × Lexicality × Time sph z	High frequency Time sph z	Cluster
Left Hemisphere											
−18	−34	60	369	Postcentral gyrus	3	9.42			3.70	8.14	1
−21	21	37	458	Middle frontal gyrus	8	8.49	3.49	2.69		5.96	5
−21	47	37	181	Superior frontal gyrus	8	5.49		4.87		4.91	5
−29	42	26	428	Superior frontal gyrus	9	8.61	3.45	2.87	3.06	6.46	1
−42	34	20	346	Inferior frontal gyrus	46	8.89	4.15	3.82	3.65	5.05	4
−41	23	12	308	Inferior frontal gyrus	45	8.75	4.69			6.43	2
−45	−10	44	430	Precentral gyrus	4	9.58	6.41	3.98		9.49	2
−51	−17	33	333	Postcentral gyrus	3	11.84	5.32	2.54		12.08	2
−49	−3	25	480	Frontal cortex	6	12.20	5.85	3.51		11.28	2
−24	−50	53	368	Superior parietal lobe	7	9.55	4.28	2.68		7.95	1
−23	−62	46	471	Superior parietal lobe	7	9.61	6.51	5.60	2.65	7.50	2
−39	−43	43	488	Inferior parietal lobe	40	10.19	5.46	5.17		7.27	2
−49	−41	22	454	Supramarginal gyrus	40	9.60	5.95	3.00		8.68	2
−43	−67	26	364	Angular gyrus	39	4.96		5.17		2.55	7
−55	−22	17	464	Superior temporal gyrus	42	9.97	4.83	2.72		10.35	2
−50	−4	7	477	Superior temporal gyrus	22	11.63	4.92	3.91		10.10	2
−40	−34	13	441	Transverse temporal gyrus	41	10.29	6.30			8.97	1
−53	−19	0	434	Middle temporal gyrus	21	9.42	3.54			8.16	2
−49	−41	9	417	Middle temporal gyrus	21	10.44	6.32			8.94	2
−51	−59	2	481	Inferior temporal gyrus	37	10.53	4.61			8.94	2
−21	−51	−7	438	Fusiform gyrus	19	9.12	5.93			7.43	1
−25	−78	22	467	Middle occipital gyrus	19	10.26	5.67	4.94		8.81	1
−33	−86	4	405	Middle occipital gyrus	18	7.50				8.02	1
−28	−88	−8	371	Inferior occipital gyrus	18	10.07	5.25	2.67		9.64	1
−33	−75	−13	459	Inferior occipital gyrus	18	10.63	6.87			9.98	2
−34	11	6	478	Insula		11.23	5.32			8.45	1
−32	14	−11	225	Insula		4.43	6.49			3.08	3
−18	−2	15	435	Caudate		10.19	6.76	4.18		7.61	1
−27	−9	3	468	Putamen		10.42	6.51	4.39	4.05	8.45	1
−23	−66	−21	423	Cerebellum		11.43	6.69	2.88		10.49	2
−28	−59	−30	378	Cerebellum		9.02	4.19	2.89		8.49	2
Interhemisphere											
−4	5	55	369	Superior frontal gyrus	6	8.34	5.98	3.51		6.97	2
8	44	40	219	Superior frontal gyrus	8	7.04	4.02	4.12	3.76	5.49	5
2	28	33	465	Superior frontal gyrus	9	8.91	4.90	3.72	4.08	7.17	1
4	44	22	328	Superior frontal gyrus	9	6.71	4.89	3.16		5.37	5
11	−54	54	391	Precuneus	7	8.62	4.38			6.15	6

Table 2. (*continued*)

X	Y	Z	Voxels		Brodmann's area	Time sph z	Length × Time sph z	Lexicality × Time sph z	Length × Lexicality × Time sph z	High frequency Time sph z	Cluster
−10	−48	52	406	Precuneus	7	9.21	3.67			7.83	6
2	−46	50	380	Precuneus	7	8.96	3.81			7.05	6
−10	−24	46	331	Paracentral lobule	5	9.30	3.82	3.36		7.51	6
2	−17	46	393	Paracentral lobule	5	9.03	4.81			7.32	1
−5	10	39	495	Anterior cingulate gyrus	32	11.56	5.68	3.05		9.78	1
2	−2	44	326	Cingulate gyrus	24	10.85	5.26	3.24		9.45	1
11	−32	41	471	Cingulate gyrus	31	9.62	3.37			7.85	6
−13	−37	40	430	Cingulate gyrus	31	9.44	3.71			7.25	6
−2	−42	31	156	Posterior cingulate gyrus	31	6.38		3.62	3.62	2.98	6
2	−56	19	231	Posterior cingulate gyrus	31	6.44	3.43	4.65		2.97	6
−15	−38	−1	409	Retrosplenium	30	9.30	5.55		3.67	6.45	2
7	−35	−1	397	Retrosplenium	30	9.72	6.41	3.41		7.13	2
−8	−69	−3	505	Lingual gyrus	18	10.86	7.00		2.66	9.79	2
−12	−88	−4	469	Inferior occipital gyrus	18	9.87	8.10	2.86	2.69	9.16	2
11	−71	12	483	Cuneus	17	9.92	7.20	4.29		8.39	2
−9	−79	9	484	Cuneus	17	10.56	7.21	3.01		9.72	2
−14	−25	5	469	Thalamus		11.99	6.05	3.47		10.02	1
14	−20	5	457	Thalamus		11.92	5.84	3.87		10.25	1
5	−54	−22	435	Cerebellum		9.39	4.85	3.94		8.11	2
2	−66	−23	445	Cerebellum		10.16	5.87	3.69		9.22	2

Right Hemisphere

X	Y	Z	Voxels		Brodmann's area	Time sph z	Length × Time sph z	Lexicality × Time sph z	Length × Lexicality × Time sph z	High frequency Time sph z	Cluster
34	31	33	350	Middle frontal gyrus	9	6.50	3.61	5.58	2.75	5.40	1
31	43	22	411	Middle frontal gyrus	10	9.08	3.83	3.64	3.44	6.53	1
44	38	21	335	Middle frontal gyrus	46	8.41	3.69	3.94	2.69	5.58	1
47	6	21	231	Inferior frontal gyrus	44	9.06	3.12	4.46		7.43	1
41	−15	39	470	Precentral gyrus	4	11.78	5.01			12.48	2
20	−33	54	472	Superior parietal lobe	7	9.18				7.85	1
24	−61	47	503	Superior parietal lobe	7	8.57	6.96	5.64		6.73	1
34	−46	47	468	Inferior parietal lobe	40	8.72	4.92	4.80		6.71	1
43	−32	46	406	Inferior parietal lobe	40	6.58	5.36	3.73		3.84	3
42	−66	20	177	Angular gyrus	39	8.43	4.64	2.86		6.46	6
32	−24	12	466	Transverse temporal gyrus	41	9.99	5.86			8.50	1
53	−14	12	427	Superior temporal gyrus	42	10.70	5.14			9.13	2
51	−32	8	467	Superior temporal gyrus	42	10.86	5.47			9.80	2
48	5	3	448	Superior temporal gyrus	22	10.51	3.70		4.11	8.43	2
45	−61	7	277	Middle temporal gyrus	37	10.30	3.85		3.54	8.44	1
58	−6	−1	340	Middle temporal gyrus	21	8.49	2.74		2.64	5.04	2
28	−72	30	409	Superior occipital gyrus	19	10.38	5.87	4.08		8.72	1

Table 2. (*continued*)

X	Y	Z	Voxels	Brodmann's area	Time sph z	Length × Time sph z	Lexicality × Time sph z	Length × Lexicality × Time sph z	High frequency Time sph z	Cluster
17	−79	27	349	Superior occipital gyrus	19	9.62	4.01	3.34		9.10	1
33	−77	18	293	Middle occipital gyrus	19	10.07	5.86	3.46		8.31	1
29	−82	5	415	Middle occipital gyrus	18	10.30	6.35	2.72	3.68	8.34	1
42	−61	−6	364	Inferior occipital gyrus	18	9.58	5.13	4.20		8.36	1
20	−84	−5	485	Inferior occipital gyrus	18	10.15	8.10			9.96	2
39	−74	0	413	Inferior occipital gyrus	18	10.15	4.34	2.99	2.50	8.96	1
19	−62	4	465	Lingual gyrus	18	9.19	6.66	2.68		8.06	2
24	−43	−3	454	Lingual gyrus	19	8.74	5.30		2.83	6.04	1
35	15	10	459	Insula		11.08	5.80	3.87	2.74	8.63	1
35	−12	6	352	Insula		10.61	4.91		3.83	9.20	1
25	1	6	484	Putamen		9.62	6.40	4.47	3.20	7.13	1
33	−57	−25	515	Cerebellum		11.11	5.95			9.87	2

sph z = sphericity-corrected z scores, where sph z 1.96 = p .05; only z scores surpassing 2.5 (p < .0124) are shown. Cluster = assigned from hierarchical clustering analysis. Washington University-based Talairach coordinates are reported here and throughout the manuscript.

replication condition had a word length range that encompassed both short and long (two to seven letters) and was intermediate in activity level between the one-syllable and three-syllable low-frequency word stimuli (Figure 2). The activity level for the high-frequency word stimuli was qualitatively very similar to that found for high-frequency word reading in adults, replicating the findings in Church et al. (2008). A borderline effect of Lexicality × Time ($z = 2.53$) was observed in the supramarginal ROI; however, it was attributable solely to the tail of the time course (i.e., MR Frames 6 and 7). When an analysis was restricted to the first five points of the time course, the effect of Length × Time remained significant ($z = 3.35, p < .001$), but the Lexicality × Time effect disappeared ($z = 0.22$). As can be seen in Figure 2, time courses for the nonword stimuli replicate the Length × Time effects shown by the low-frequency words, with three-syllable nonwords resulting in greater activity than one-syllable nonwords (Figure 2). When the mean bigram frequency of stimuli was regressed out of this analysis, the Length × Time effect remained significant ($z = 5.86, p < .0001$). When reaction time was separately regressed out of this analysis, the Length × Time effect remained significant ($z = 3.30, p < .001$), but the Lexicality × Time effect was reduced below significance ($z = 1.16$).

The angular ROI showed a considerably different profile of results. The dynamic range of the BOLD response, which was previously shown to be positive in children and flat in adults for high-frequency words at those coordinates (Figure 1; Church et al., 2008), showed only a negative deflection from baseline in the adults for the current stimulus sets (Figure 2). Also, in contrast to what was observed in the supramarginal ROI, the angular gyrus did show a sig-

nificant effect of Lexicality × Time ($z = 3.74, p < .0005$), with a marginally significant effect of Length × Time ($z = 2.53$) and an interaction effect of Length × Lexicality × Time ($z = 2.82, p < .005$). The tails of the time courses did not drive these effects. The low-frequency word stimuli resulted in negative BOLD activity compared with baseline, and the nonword stimuli resulted in even more negative changes in BOLD activity, particularly for three-syllable nonwords (Figure 2). The high-frequency word replication condition was, qualitatively, flat to slightly negative and did not result in significant activity in the angular ROI by our threshold of a z score of 2.5 ($z = 2.35$). When the effect of mean bigram frequency was regressed, the Lexicality × Time effect remained significant above our threshold ($z = 3.57, p < .001$), whereas the Length × Time and the Length × Lexicality × Time effects did not ($z = 2.39$ and 1.98, respectively). When the effect of reaction time was regressed out of the analysis, the Lexicality × Time effect remained significant ($z = 3.31, p < .001$), as did the Length × Lexicality × Time interaction ($z = 2.64, p < .01$), but the Length × Time effect was reduced below our threshold ($z = 2.34$). Overall, the nonword conditions continued to show greater negative deflection than the word conditions (data not shown).

The left fusiform region (VWFA ROI), which was close to the classically described putative VWFA, was previously shown to be stronger in children than adults for high-frequency word reading. In this analysis, this region was different from the other two applied regions, such that there were effects of Length × Time ($z = 4.33, p < .0001$) and Lexicality × Time ($z = 3.06, p < .005$), but there was no significant three-way interaction. When mean bigram frequency was used as a regressor, the Length × Time

Figure 2. Applied ROIs. Time courses for all five conditions in (A) the applied left supramarginal ROI (left time courses) (−52, −42, +24), (B) the applied left angular ROI (top right time courses) (−49, −62, +29), and (C) the applied left VWFA ROI (bottom left time courses) (−38, −60, −12). In adults, the supramarginal ROI shows a significant effect of Length × Time, such that longer stimuli result in greater activity. The angular ROI shows a significant effect of Lexicality × Time, Length × Time, and Length × Lexicality × Time interaction, such that nonword items, particularly three-syllable nonwords, result in greater negative activity than low-frequency words. The VWFA ROI shows a significant effect of Length × Time and Lexicality × Time, with no three-way interaction.
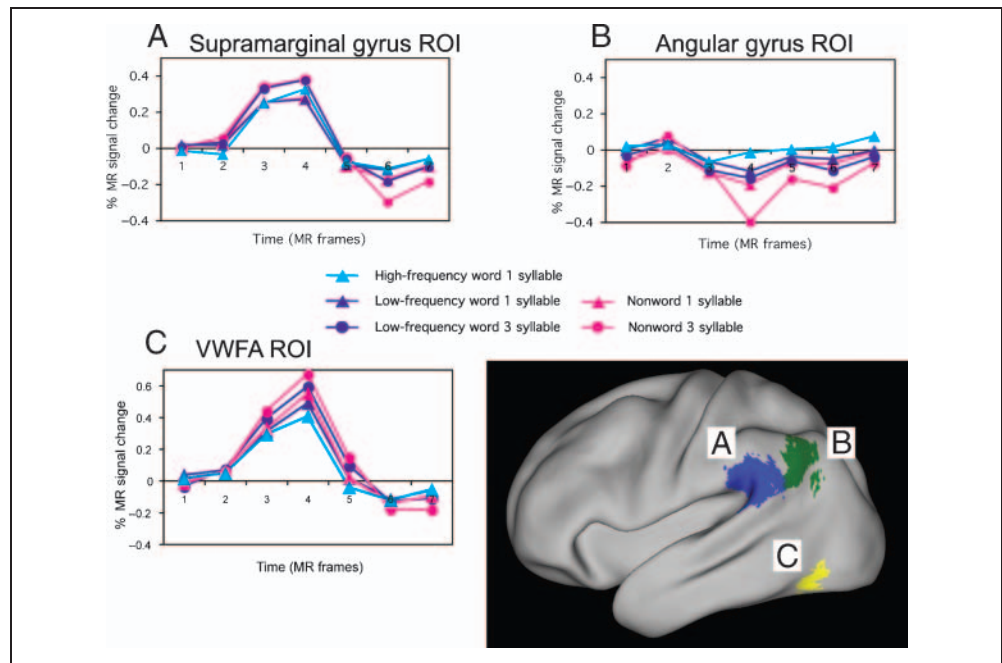
Figure 3. Length × Time, Lexicality × Time, and Length × Lexicality × Time effects at different z score thresholds.
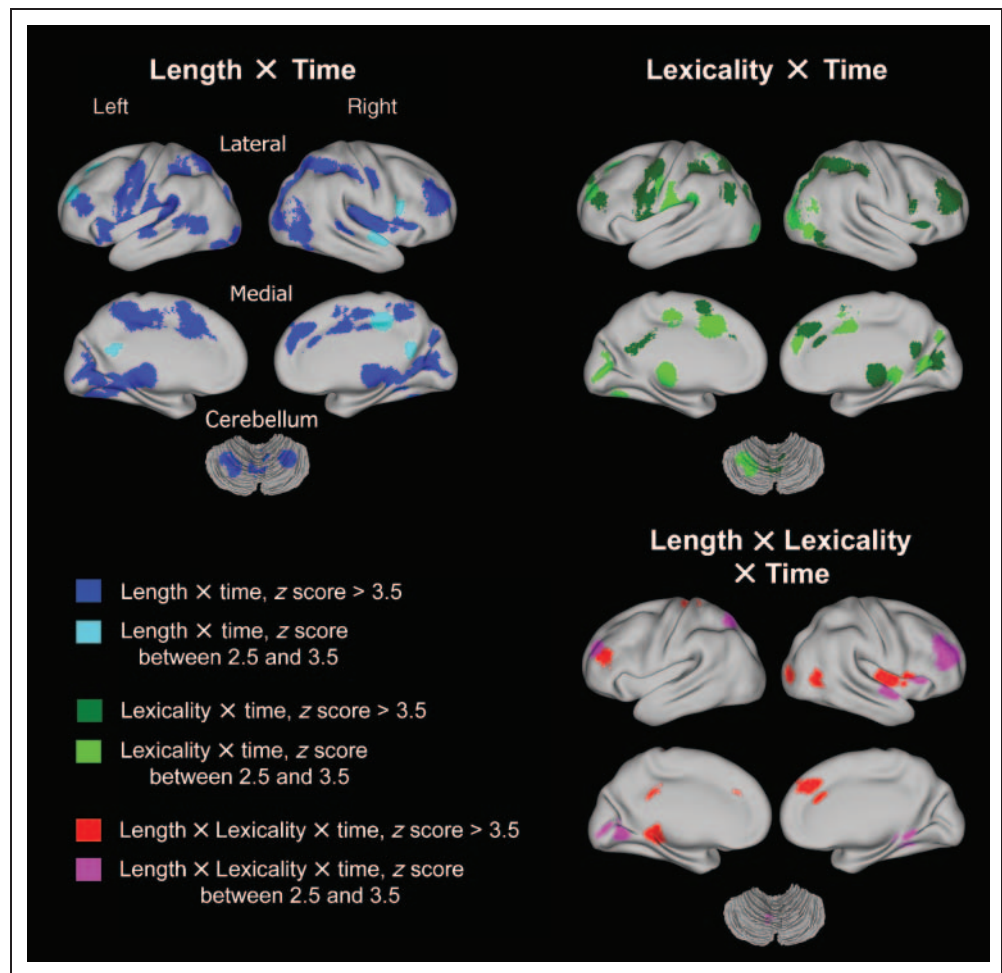
Figure 4. Hierarchical clustering of the 85 regions from concatenated time courses of all five conditions averaged across subjects. Eighty-five regions were used in the hierarchical clustering analysis, producing seven clusters at a threshold of 0.1. The colors of the clusters match the colors of the regions on the brain. Cluster 7 (black) was a single region and was negatively correlated (shown as >1 value) with the rest of the regions. See text for details.
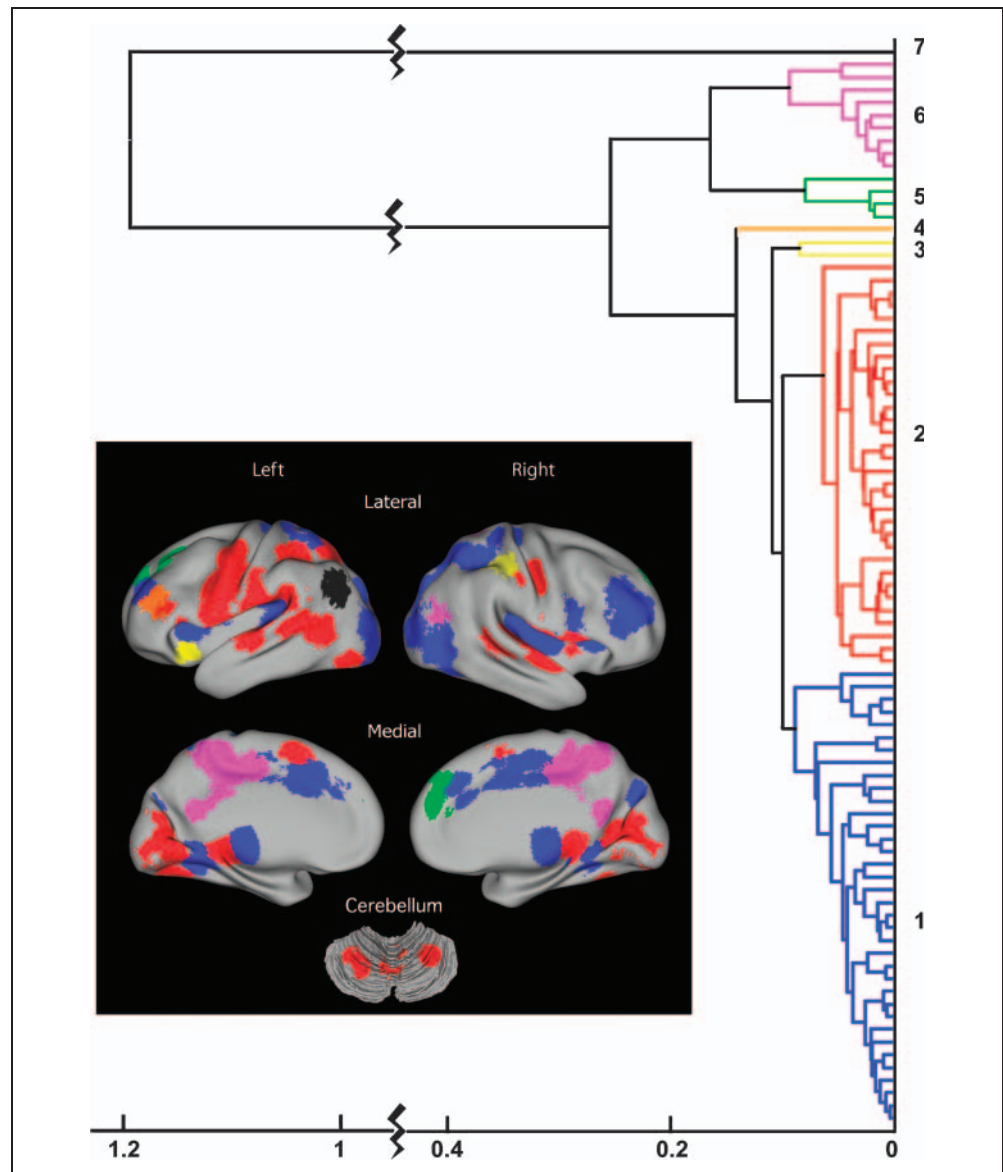
and the Lexicality × Time effects remained significant ($z = 4.43, p < .001; z = 3.17, p < .001$, respectively). This VWFA ROI appears to be strongly affected by reaction time, such that when reaction time is used as a regressor, no effects pass our threshold and only a weak effect of Length × Time remains ($z = 2.05$). The time courses in this region build upon one another such that one-syllable high-frequency words have the smallest magnitude of signal change and three-syllable nonwords have the largest change (Figure 2).

Whole-brain Analyses

The set of 85 significant regions had a variety of statistical effects (Table 2). Many regions were considered active (greater than a z score of 2.5) for more than one effect (Figure 3). Many of these regions retained their statistical effects when reaction time was used as a regressor (see Supplemental Information). This threshold approach, although somewhat informative, did not illuminate any particular ROIs as so many had similar effects (and similar appearing time course relationships). Thus, hierarchical clustering was employed to draw out regional differences.

Hierarchical clustering of the 85 region set resulted in some useful divisions and produced a strong goodness-of-fit measure to the data (cophenetic $r = .909$). At a threshold of the distance metric $(1 - r) = .1$, seven clusters were apparent (Figure 4). These clusters had some consistency of anatomical location and isolated some regions of particular interest in the existing literature on reading development.

Most striking was the negative correlation formed between a region in the left angular gyrus (Cluster 7) and all other regions. This region's concatenated time course was different (i.e., negative deflection or deactivation) from any other region (Figures 4 and 6). This angular gyrus region captures the same lexicality effect as described in the applied angular ROI and is highly overlapping in location (see ROI analyses section). Another region in the whole-brain analysis

was similar to the applied supramarginal ROI (see ROI analyses section). This supramarginal region (−49, −41, +22) was assigned to Cluster 2 and captured similar statistical effects as the applied supramarginal ROI (significant effect of Length × Time, significant effect of Lexicality × Time limited to the tail of the time course).

The clusters differed in time course shape (Figure 5). Regions in Cluster 1 ($n = 36$ regions) had a significant effect of Length × Time, and some regions also had a significant Lexicality × Time or a significant Length × Lexicality × Time effect. The majority of these regions peaked at Time Point 3. The time to peak of the time courses is an interesting difference from Cluster 2 ($n = 32$ regions), which contained regions with a similar assortment of statistical effects, but the majority of these regions peaked at Time Point 4. There was a reliable difference between Cluster 1 and Cluster 2 (cluster as a between-group measure in a repeated measures ANOVA of the concatenated time courses, using the individual regions assigned to each cluster as the independent observations; SPSS: $p < .00001$; $F = 62$).

The two regions in Cluster 3 had few commonalities, although they both show an effect of length and both show a flat peak across Time Points 3 and 4. The sole region in Cluster 4 was significant (z score > 3.5) for all effects (Length × Time, Lexicality × Time, Length × Lexicality × Time, main effect of time for high-frequency words).

Cluster 5 ($n = 4$ regions) had highly similar time courses (narrow peaks and similar patterns) despite varying statistical effects. Cluster 6 ($n = 9$ regions) contained regions that had relatively strong negative deflections in the tails of the time courses and largely had only length as a significant statistical effect. Clusters 3–7 are shown in Figure 6.

The effects of regressing reaction time and separately the mean bigram frequency on the clustering results were examined (see Supplementary information). In brief, the clustering results were robust to these regressions; 8 of the 85 regions (9%) changed cluster assignment when the mean bigram frequency was regressed, and only 5 of the 85 (6%) regions changed cluster assignment when reaction time was regressed.

DISCUSSION

Length and Lexicality Manipulations Each Produce Widespread Changes in Brain Activity

The whole-brain analysis of this experiment resulted in a large set of regions showing many overlapping effects of
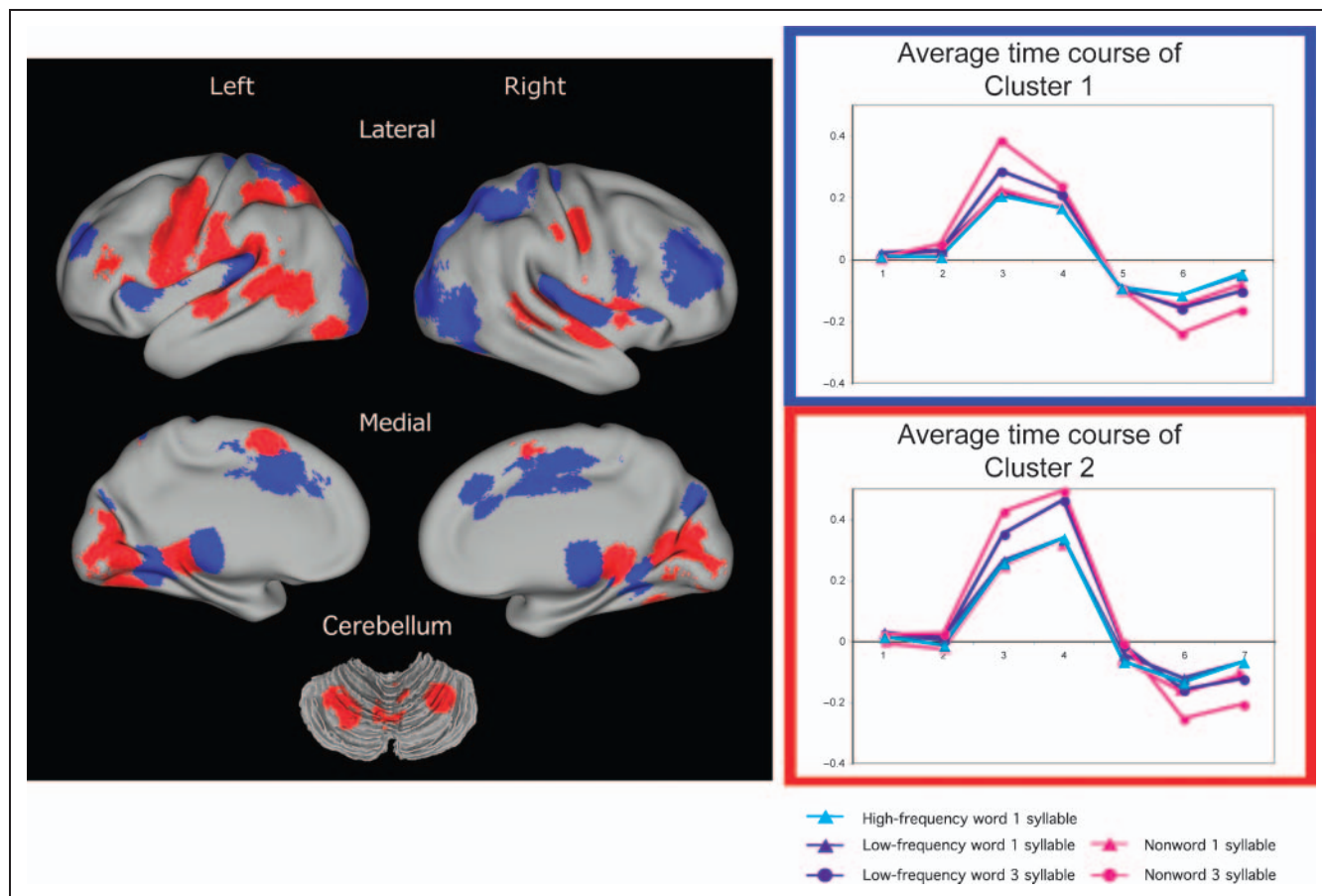
Figure 5. Cluster 1 (blue regions) and Cluster 2 (red regions) peak at different time points. The average time courses for each condition across all of the regions within a cluster are shown at right. The box around the time course corresponds to the color of the cluster and the regions. Time (in MR frames) is the *x*-axis, whereas % BOLD signal change is the *y*-axis.
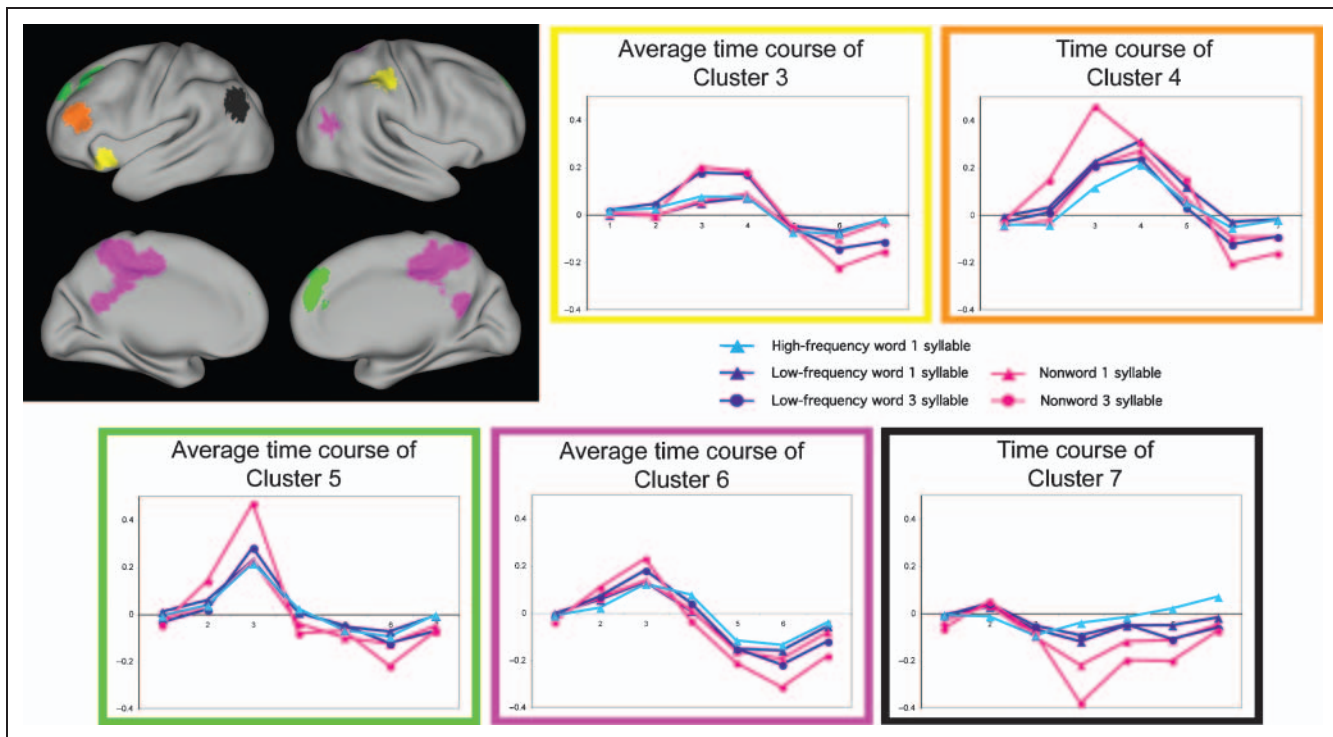
Figure 6. Clusters 3–7 reveal different time courses for different anatomical locations. The average time courses for each condition across the regions within a cluster are shown at right. The box around the time course corresponds to the color of the cluster and the regions. Time (in MR frames) is the *x*-axis, whereas % BOLD signal change is the *y*-axis. Cluster 3 (yellow; 2 regions); Cluster 4 (orange; 1 region); Cluster 5 (green; 4 regions); Cluster 6 (pink; 9 regions); Cluster 7 (black; 1 region).

varying statistical significance. Length effects were observed in motor-related regions in addition to visual, temporal, midline, and frontal regions. Regions demonstrating lexicality effects were highly overlapping with those showing length effects, and the time course peak amplitudes often paralleled reaction times, with the three-syllable nonword stimuli resulting in the longest RT and the largest BOLD magnitude. By examining the regions where there were nonoverlapping effects between length and lexicality, some interesting locations emerge.

First, the left angular gyrus region (also discussed below as a specific ROI) shows a significant effect of lexicality but does not show a significant effect of length. This lexical-only effect was not seen in other purported default mode network regions (regions that show greater activity for fixation than tasks; Raichle & Mintun, 2006; Fox et al., 2005; Gusnard & Raichle, 2001; Shulman et al., 1997), including the right angular gyrus, suggesting that this region in the left angular gyrus is uniquely involved in adult reading. Interpretation of the negative activity for this region and its role in reading is not straightforward and is discussed further below.

Regions that had a strong effect of length but lesser or no effect of lexicality were predominantly in the temporal lobes, involving presumed auditory regions, including the superior and the middle temporal gyri. Despite the small effect of lexicality shown in Figure 3 for a region in the left supramarginal gyrus, a hypothesized phonological processor, this effect was driven entirely by the tail of the time

course, as described for the similar applied supramarginal ROI. Thus, auditory and putative phonological processing in this region appears to be largely insensitive to effects of lexicality, supportive of phonological processing occurring there regardless of stimulus type.

It is important to note that our stimuli, although matched for length, were not controlled for other variables such as orthographic neighborhood and bigram frequency. The length (in number of letters) of our stimuli was highly correlated with summed bigram frequency (.839, $p < .0001$) and negatively correlated with orthographic neighborhood ($-.71, p < .0001$), consistent with their natural relations in the language (see Balota et al., 2004). Future work may be able to better separate these elements from length effects, and we refer readers to an article describing a method with which to tackle this issue (Graves et al., 2009).

Hierarchical Clustering Reveals Functional Relationships from Time Course Patterns

Ultimately, statistical threshold cutoffs impose a dividing line with which to make categorical distinctions of, in our case, length and lexicality effects. However, ignoring regions with effects just below the threshold may lose some information. Furthermore, visual inspection of these thresholded effects may not provide any information about timing or help in deciphering key regional distinctions. We thus used another technique, hierarchical clustering, to explore

whether additional information could be discerned about the effect of the implemented stimulus manipulations on regional brain activity.

Using hierarchical clustering, divisions revealed clear differences in time course shape, despite overlapping statistics. These clusters provide information about regional similarities and interactions that may lead us to further insights about regional roles.

In the case of the largest clusters (Clusters 1 and 2), Cluster 1 time courses generally have peaks at Time Point 3 (approximately 6 sec after stimulus presentation), whereas Cluster 2 time courses generally have maximum peaks at Time Point 4 (approximately 9 sec after stimulus presentation). Cluster 1, generally includes putative task control regions (cingulate, bilateral anterior insula, thalamic, and parietal regions), regions in temporal cortex, and regions in dorsal and lateral occipital cortex. Cluster 2 includes regions in motor cortex, temporal cortex, ventral and medial occipital cortex, and cerebellum. The difference in signal timing of these regions suggests a possible ordering of activity in these regions such that regions in Cluster 1 may be more involved in control or early stage processing, whereas regions in Cluster 2 involve more later stage processing, involving "primary" input and output cortex.

We speculate that the later peaking of activity in primary processing regions may reflect a role for late recruitment of some regions. It is interesting to note the medial occipital cortex regions, located near primary visual cortex, have large magnitude time courses that are high at Time Point 3 but ultimately peak relatively late at Time Point 4. Their peak at Time Point 4 is concurrent with the activity peaks observed in motor and auditory cortex. The difference in peak timing may reflect the output from control processing regions that feeds back onto some sensory processing regions in parallel with information moving forward to response or output processing regions. Another alternative is that the regions are clustering on the basis of some vascular feature. Given that the cluster assignments group regions across vascular distributions and that adjacent regions can be seen to cluster differently, we find a vascular argument unlikely (Church, Petersen, & Schlaggar, 2010).

Hierarchical clustering also identified a region acting very differently compared with all of the other regions during reading: Cluster 7, a region in the left angular gyrus, was the sole constituent of this cluster. This region, as discussed above, has significantly negative time courses for the low-frequency and nonword conditions with a strong effect of lexicality (Figure 6). Negative time courses during task activity are hallmark of regions of the default mode network. The default mode network as proposed by Raichle and Mintun (2006), Fox et al. (2005), Gusnard and Raichle (2001), and Shulman et al. (1997) comprises a set of regions in adults that show decreases from baseline in a wide variety of tasks. These regions include posterior cingulate, medial prefrontal cortex, other frontal regions, and regions in the same general location as the left angular gyrus ROI reported here (Fox et al., 2005). What is particularly in-

triguing about this region is that other regions that may be close to members of the default mode network (e.g., the posterior cingulate and right angular gyrus regions; Table 2) do not show this same pattern of effects, but rather show positive activity followed by strong negative tails. These other presumed default mode network members cluster together (Cluster 6) and are negatively correlated with the left angular gyrus region. The left angular gyrus is discussed further below.

Magnetoencephalography studies provide more detail regarding the timing of activity in regions involved in word reading (e.g., Simos et al., 2009; Wydell, Vuorinen, Helenius, & Salmelin, 2003). Similar to the present study, Wydell et al. (2003) found no unique regions for reading of words versus nonwords and earlier peaks in posterior occipital cortex than temporal cortex, despite the vastly different time scales of the two types of measurements. Simos et al. (2009), however, found differences in timing during a lexical decision task between several regions that we see cluster together in Cluster 2: ventral occipital cortex, premotor cortex, and superior temporal cortex. Obviously, BOLD data are slow and not as ideal for studying timing differences as magnetoencephalography, but we believe this type of clustering approach may still be helpful to future investigations of reading by highlighting different patterns of results across the brain that are difficult to observe by eye or by statistical threshold.

VWFA Shows Increased Activity for Both Length and Lexicality Manipulations

Surprisingly, no region within 1 cm of the purported VWFA region (Cohen & Dehaene, 2004) came out of the whole-brain analysis. This seemingly negative result may be a limitation of our peak-finding software, or it may be indicative of widespread activity in the extrastriate cortex that is not necessarily peaking at a specific VWFA region. The closest extrastriate region to come out of the whole-brain analysis was located at (-51, -59, 2) and was part of Cluster 2. Statistically, this region showed only an effect of Length × Time above our threshold ($z = 4.61, p < .0001$). To explore the putative ventral processing stream further, we applied a VWFA ROI, and the region showed a stacked profile of time courses, layered according to task difficulty (Figure 2). This applied VWFA ROI had a Length × Time effect, which is perhaps contrary to the hypothesized parallel processing aspect of the lexical route proposed by the dual route cascade model of word reading (Coltheart et al., 2001). Activity was strong in this region for all stimuli, with the nonwords resulting in slightly larger activity compared with the same-length word stimuli, creating a significant Lexicality × Time interaction, with no interaction of Length × Lexicality × Time. Thus, we did see a lexicality effect as we hypothesized, with an increase in activity with unfamiliar stimuli as has been reported by many others (Bruno et al., 2008; Kronbichler et al., 2004, 2007; Mechelli et al., 2003). The sensitivity to both length and lexicality

manipulations within the VWFA ROI suggests that some sublexical processing may occur in this region. The stacked profile of time courses may reflect an effect of familiarity, with the high-frequency words resulting in the smallest amount of activity and the three-syllable nonwords resulting in the highest amount of activity. However, the VWFA ROI lost both the Lexicality × Time and the Length × Time effects when reaction time was regressed out, suggesting the effects observed in this region were strongly related to reaction time (data not shown).

Neighboring Regions in the Angular and Supramarginal Gyri, Despite Being Similar in Children for High-frequency Words, Diverge in Adults with Length and Lexicality Manipulations

Left Supramarginal Gyrus Activity Is Consistent with a Phonological Processor

The data from the supramarginal ROI are most consistent with a phonological processing role in reading. This region has greater activity in children than adults for reading high-frequency words (Church et al., 2008). It is sensitive to length manipulations in adults (Figure 2) consistent with a serial phonological conversion process or an increase in phonological processing demand with length (Rastle & Coltheart, 2006; Coltheart et al., 2001). The lack of a Lexicality × Length interaction in activity for this region, as might be predicted by dual-route cascade models and as observed in the reaction times, suggests that any benefit of processing through lexical or orthographic–semantic pathways for words may not be reflected within this phonological processor itself. It may be that the Length × Lexicality interactions observed behaviorally (Weekes, 1997) are the result of different processing for words than nonwords in other regions or in the interaction of this region with other parts of a reading network.

The differences observed between adults and children for reading also suggest that reliance on phonological processing declines for familiar words over age, as suggested by many groups (e.g., Schlaggar & McCandliss, 2007; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003; Pugh et al., 2001), but that this decrease in positive activity is "reversible" in adults with more phonologically demanding stimuli. The present study demonstrates that hypothesis-driven manipulation of stimulus properties can drive activity in a region and provides converging evidence for a role in phonological processing in the supramarginal gyrus.

Left Angular Gyrus Activity Is Negative during Task Trials and Is Inconsistent with a Role in Phonological Processing

Unlike activity in the supramarginal ROI, activity observed in the angular ROI did not conform to expectations, diverging in several ways from both the supramarginal ROI results

and from a role in phonological processing. When adults were presented with the more phonologically challenging lexical stimuli, activity in this region showed a negative dynamic range, with greater negative change for nonword than word stimuli.

This finding, coupled with the previously reported positive activity in children, suggests that the angular ROI may, over the course of development, transition into being a member of the "default mode network." If the angular ROI being studied here is, in fact, part of the default mode network as was discussed earlier, then the surprising finding is the positive activity observed in children reading high-frequency words (Church et al., 2008).

To date, few studies have described the functional development of the default network (Fair et al., 2008; Thomason et al., 2008; Buckner et al., 2006; Marsh et al., 2006). The results reported here suggest that at least this left angular ROI may, with age, transition from generally positive activity dynamics in children to negative activity in adults. Several regions have shown activity decreases with age in at least one previous study, but these regions typically progress, with age, from positive to less positive or positive to no effect (Brown et al., 2005).

Thus, the totality of results in the angular ROI does not illuminate a straightforward functional ascription. At coordinates close to the angular ROI reported here, Binder et al. (2005) reported greater word than nonword activity in adults and consequently suggested that this region is involved in semantics (see also Demonet et al., 1992). However, it is possible that relative to a zero baseline, greater negative activity was being subtracted from less negative activity (instead of less positive being subtracted from more positive), thus making interpretation less clear. Figure 3 of that article suggests that nonword activity is negative relative to fixation as we see here, and the greater activations for words relative to nonwords seems to draw out the primary members of the default network (Binder et al., 2005). Similarly, a semantics hypothesis has been forwarded in other articles that report negative activity in this general region (Mechelli, Josephs, Lambon Ralph, McClelland, & Price, 2007; Frost et al., 2005). There is further discussion of the semantics and default mode network overlap elsewhere (Binder et al., 2009; Graves et al., 2009). Although overall our results are consistent with other studies and a semantic hypothesis, the negative activity observed requires care in assigning a particular processing role to the angular gyrus.

Specifically, interpreting less negative activity for a given condition as indicative of greater engagement of a process (e.g., greater engagement of semantic processing in the angular gyrus) implies that something causing even less negative activity (i.e., simply visually fixating and not processing words) engages that process even more than the active condition. This scenario would mean that semantic processing is more demanding at rest than when overtly reading words. Although possible, it seems reasonable to suggest that the dynamic range of BOLD activity in a region

must be considered when ascribing a processing role to a region. Considering a negative dynamic range of activity for a region as equivalent to a positive dynamic range of activity may be misleading and should be done with caution (discussed in more detail in Church et al., 2010).

The positive angular gyrus activity shown by children for high-frequency word reading, then, is a finding worthy of more research and suggests that when learning to read, children recruit resources not used by adults (or that are even actively suppressed in adults). Furthermore, these results suggest that future experiments should explore whether this positive activity in children is reading specific. One way to address this issue would be to apply the non-word and low-frequency word stimuli given to adults in the current study to children, although this task would be relatively more difficult because of their early reader status and their potential inability to provide requisite task performance.

Reaction Times Do Not Drive Effects

An observation from the ROI application is that when reaction time was regressed out of the analysis, the primary effects in the supramarginal and angular ROIs remained significant. Thus, it is unlikely that the effects observed in these regions are being driven purely by a reaction time effect. This result is consistent with recent analyses of reaction time effects in reading in adults (Graves et al., 2009; Binder et al., 2005), which report reaction time effects primarily in frontal, insular, anterior cingulate, and superior parietal regions, but not these regions.

Developmental Results Drove This Analytic Approach

An overall point of this study is that developmental and adult studies are mutually informative. Developmental results can lead to probing the nature of the mature system (its flexibility, activity dynamics, etc.), and developmental studies can reveal the path taken to the mature form (used a lot to used less, used to inhibited, etc.). The decreased activity observed in adults compared with children in the supramarginal and angular regions led to this study design, which was successful in driving activity of the left supramarginal ROI, and led to surprising results in the left angular ROI.

Employing relatively new analytical strategies, including functional connectivity analyses, for the default mode network, these two ROIs and other reading regions during task performance (e.g., Bitan et al., 2005; Mechelli et al., 2005) and at rest (e.g., Koyama et al., 2010; Vogel et al., 2009; Dosenbach et al., 2007; Fair et al., 2007; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Fox et al., 2005) may better clarify the processing changes of reading-related regions over development. In particular, it is of great interest to identify why these two neighboring parietal processing regions (the supramarginal gyrus and the angular gyrus regions) change in activity across development because

such knowledge may be relevant to a neuropedagogy of reading and dyslexia remediation.

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