Selectivity and Development of the Visual Word Form Area

By

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Abstract

An area of left occipitotemporal cortex commonly referred to as the visual word form area (VWFA), has consistently been shown to activate during the processing of written language. However, the exact nature of the region's selectivity is still under debate. In this thesis, I explore the selectivity of the visual word form area at three different levels. First, I examine whether the VWFA differentiates between letter strings of different lexicality and pronounceability and argue that the VWFA's selectivity is greatly influenced by attention. Second, I explore the developmental course of mirror discrimination in the VWFA, and show that children do not display adult-like mirror discrimination of letters even into early adolescence. Finally, I look at the developmental course of VWFA selectivity for words compared to nonlinguistic visual stimuli. While children have adult-like activation patterns when words are compared to a low-level visual control, they show less specialization compared to adults when objects are used as a control.

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Chapter 1: Introduction

Background

The study of early visual word processing in the brain has focused primarily on the left occipitotemporal region, an area commonly referred to as the visual word form area (L. Cohen & Dehaene, 2004; McCandliss, Cohen, & Dehaene, 2003). Meta-analyses have found that region activates reliably to visually presented words (Jobard, Crivello, & Tzourio-Mazoyer, 2003), and that activation is consistent across tasks and different types of writing systems (both phonetic and logographic) (Bolger, Perfetti, & Schneider, 2005; Tan, Laird, Li, & Fox, 2005). The region displays several characteristics useful for visual word processing, including location invariance, the ability to generalize across letter case (Cohen & Dehaene, 2004; Dehaene et al., 2001, but see Rauschecker, Bowen, Parvizi, & Wandell, 2012) and a preference for known scripts over unknown scripts (Baker et al., 2007).

Several lines of evidence suggest a critical role for the region in reading. Lesion evidence has shown that damage to the left fusiform results in reading impairments and pure alexia (L. Cohen et al., 2003; Gaillard et al., 2006; Leff, Spitsyna, Plant, & Wise, 2006; Pflugshaupt et al., 2009; Philipose et al., 2007; Randi Starrfelt, Habekost, & Leff, 2009). Imaging studies have also found links between VWFA activation and literacy in adults. Reading ability is both positively correlated with activation to words (Dehaene, Pegado, Braga, Ventura, & others, 2010;

Shaywitz et al., 2002) and negatively correlated with activation to non-word stimuli (faces) in both adults and pre-reading children (Cantlon, Pinel, Dehaene, & Pelphrey, 2011; Dehaene, Pegado, et al., 2010)

Short-term laboratory training provides supporting evidence for the link between VWFA activation and reading acquisition. One study trained pre-reading children on grapheme-phoneme correspondences for approximately two months and found that VWFA specialization for words (compared to false fonts) increased after training (Brem et al., 2010). In adults, phonological training of an unknown script also produces VWFA activation, as did training that associated novel characters with known English letters (Song, Bu, Hu, Luo, & Liu, 2010; Xue, Chen, Jin, & Dong, 2006). The cross-modal phonological component seems to be an important factor in training studies; another study in which participants received purely visual exposure to unfamiliar characters found decreased activation for trained characters (Xue & Poldrack, 2007). A final training study found that activation in the visual word form area while viewing novel characters predicted subsequent memory for the characters (Gui Xue et al., 2010).

The link between occipitotemporal activity and reading extends into reading impairment. Children with dyslexia do not show the normal gradients of print and orthographic tuning in the left ventral visual stream displayed by normal-reading children (Van der Mark et al., 2009). The region also shows a different developmental trajectory in impaired readers. In readers with dyslexia performing a phonological processing task, the left posterior medial occipitotemporal region becomes more active with age, compared to the left anterior lateral occipitotemporal region in normal readers (Shaywitz et al., 2007).

While fMRI experiments do not have the temporal resolution to provide information on the time course of VWFA activation, magnetoencephalography (MEG) and electroencephalography (EEG) localization suggest that the left occipitotemporal region processes words about 150-200ms after stimulus onset and gives rise to a posterior negativity known as the N1 or N170 component (Maurer, Brandeis, & McCandliss, 2005; Maurer, Brem, Bucher, & Brandeis, 2005; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999). In normal reading adults, the N1 component is tuned for words and has a larger amplitude for words than symbols. Prereading kindergarteners do not show this N1 specialization (Maurer, Brem, et al., 2005), although second graders display a stronger specialization compared to adults (Maurer et al., 2006). In second graders with dyslexia, this specialization was decreased compared to normal readers (Maurer et al., 2007).

Current Directions in VWFA Research

Research on the visual word form area has focused on several key questions. One line of research explores the nature of the representations in the VWFA, as well as the region's selectivity. Much research has been conducted on whether the region encodes information such as orthographic regularity, (Binder, Medler, Westbury, Liebenthal, & Buchanan, 2006; Vinckier et al., 2007), lexicality (Glezer, Jiang, & Riesenhuber, 2009), and word frequency (Kronbichler et al., 2004). While early research focused on the VWFA as a single area, some researchers have now moved toward viewing the length of the ventral visual stream as hierarchical cascade, with each subsequent level sensitive to more complex stimulus characteristics (line segments, to letters, to bigrams, etc.) (Dehaene, Cohen, Sigman, & Vinckier, 2005).

A related direction of inquiry focuses on VWFA specialization for words compared to other classes of visual stimuli such as objects. The region is not purely a word processing area and has been shown to be active for nonreading tasks such as color naming, picture naming, reading Braille, and attending to auditory words (Buchel, Price, & Friston, 1998; Dehaene, Pegado, et al., 2010; Price & Devlin, 2003; Reich, Szwed, Cohen, & Amedi, 2011; Randi Starrfelt et al., 2009; Yoncheva, Zevin, Maurer, & McCandliss, 2009). The question remains, however, whether the VWFA responds more strongly to words than other stimuli. Some studies have found evidence for word vs. object specialization (Baker et al., 2007; Szwed et al., 2011), but other studies contest the claim (Wright et al., 2008).

Another matter of debate has been over how best to characterize the region's function. Research on VWFA selectivity has primarily viewed it as a bottom-up and stimulus driven area. Another view of the region, however, focuses on its role in integrating bottom-up visual information with top-down linguistic and semantic information. Proponents of this view point to evidence that semantics and lexicality affect activation level, suggesting both top-down and bottom-up effects (Devlin, Jamison, Gonnerman, & Matthews, 2006; Twomey, Duncan, Price, & Devlin, 2011). They also note that simple dimensions such as bigram/trigram frequency or familiarity by itself cannot explain common patterns of VWFA selectivity (Price & Devlin, 2011). Finally, the finding that cross model priming between words and pictures results in the same magnitude of repetition suppression as unimodal (word-word/picture-picture) priming suggests a large role for top-down influence in the region (Kherif, Josse, & Price, 2011).

The third direction of research takes advantage of the recent advances in developmental neuroimaging. Because reading has only existed as a cultural invention for a few thousand years (Dehaene, 2009), it is unlikely to have been shaped directly by evolutionary processes. It thus provides a unique way to study the formation of a specialized brain region based purely on learning and experience.

Outline of Dissertation

The sections of this dissertation touch on all three of the aforementioned research directions and explore three different levels of selectivity in the visual word form region.

The first experiment looks at specialization at the most fine-grained level and revisits the question of whether the VWFA distinguishes between letters strings of different lexicality and orthographic regularity. Experimental results on this topic have been mixed, and in this study we explore the role of task and attention on VWFA selectivity, as well as the implications for future research.

The second study looks at a different form of specialization, that of letters compared to mirror-reversed letters. Because letters are one of the few visual stimuli for which mirror orientation is important, some researchers have suggested that the visual system must unlearn mirror generalization in order to correctly process words. In our study, we look at the brain basis of letter reversal in children and adults to investigate the developmental course of mirror generalization while viewing letters.

The last experiment looks at specialization for words compared to objects in children and adults. We revisit the debate of whether the visual word form area is actually specialized for words compared to other categories. In addition, we look at the developmental course of the specialization to see how this changes with age.

Chapter 2: Visual Word Form Area Selectivity for Print is Attention-Dependent

Introduction

A fundamental goal for many neuroimaging studies has been to reveal the processes mediated by the VWFA. One approach has been to characterize coarse stimulus selectivity. This approach has been inspired by prior neuroimaging studies that discovered occipital-temporal regions selective for some kinds of stimuli relative to other stimuli, such as faces (the fusiform face area or FFA) (Kanwisher, McDermott, & Chun, 1997), places (the parahippocampal place area or PPA) (Epstein & Kanwisher, 1998), and bodies (the extra-striate body area or EBA) (Downing, Jiang, Shuman, & Kanwisher, 2001). Many have asked whether the specialization of these regions reflects evolutionary and genetic influences on the organization of high-level vision for kinds of percepts that have long had importance, such as recognition of people (faces) and locations (places). In contrast, reading and writing are relatively recent cultural inventions that blend human skills in language and vision, and correspondingly twin studies suggest less genetic influence on the location of the VWFA (Polk, Park, Smith, & Park, 2007).

Characterization of the VWFA's role in reading has followed two approaches. One focuses on the region as part of a bottom-up visual cascade, in which the neurons in the region are tuned to increasingly complex categories of orthographic stimuli (Dehaene et al., 2005). Prior studies have compared i) words to pronounceable nonwords (pseudowords) to discover if the VWFA responds selectively to known words, ii) words to unpronounceable letter strings to discover if the VWFA responds selectively to letter strings that obey phonological principles, and iii) words to false or foreign fonts to discover if the VWFA responds selectively to known letters.

The findings in these kinds of studies have been remarkably heterogeneous. For example, many studies find more activation to unfamiliar but pronounceable pseudowords and pseudo-homophones than to words (Bruno, Zumberge, Manis, Lu, & Goldman, 2008; Kronbichler et al., 2007; Van der Mark et al., 2009), while others find no difference (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002). Likewise, some studies find more activation in the region for strings with greater bigram frequency (Binder et al., 2006; L. Cohen et al., 2002; Petersen, Fox, Snyder, & Raichle, 1990), while other studies found no preference for greater bigram frequency (Baker et al., 2007; L. Cohen et al., 2003). Responses to words compared to false-fonts are perhaps most varied, with results ranging from greater activation or sensitivity for words than false-fonts (Petersen et al., 1990) to the opposite pattern of greater activation for false fonts than words (Reinke, Fernandes, Schwindt, O'Craven, & Grady, 2008; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003)

This variability in results is likely due to several factors. Studies differ in their definition of the VWFA, using such varied contrasts as words > checkerboards (L. Cohen et al., 2002), words > objects (Baker et al., 2007), letters > faces (Puce, Allison, Asgari, Gore, & McCarthy, 1996), words > falsefonts or foreign scripts (Barton, Fox, Sekunova, & Iaria, 2009; Fiebach, Rissman, & D'Esposito, 2006), or words/pseudowords vs. consonant strings (Devlin et al., 2006; James, James, Jobard, Wong, & Gauthier, 2005). Also, there is evidence that rather than there being a single VWFA, there may be continuum of specialization that varies as a gradient along the length of the occipital temporal reading region (Brem et al., 2006, 2009; Van der Mark et al., 2009; Vinckier et al., 2007). Other possible factors contributing to different experimental results include rate of stimulus presentation (L. Cohen et al., 2003) and word frequency (Kronbichler et al., 2004).

Another potential factor toward this variability lies in an alternative approach to VWFA function – rather than a focus on VWFA function as a bottom-up process, this approach emphasizes the synthesis of bottom-up visual information and top-down feedback from phonological and semantic regions (Price & Devlin, 2011). In this account, non-stimulus factors such as the task performed with the stimulus become important. This is noteworthy because a variety of tasks have been used to characterize stimulus selectivity in the region, including passive viewing (L. Cohen et al., 2002; Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Polk et al., 2011; Puce et al., 1996), comparison of current and just-prior stimuli (one-back) (Baker et al., 2007; James et al., 2005; Szwed et al., 2011; Wright et al., 2008), same-different matching (Polk et al., 2011), letter detection (Turkeltaub et al., 2003), reading aloud (Kherif et al., 2011), masked priming (Dehaene et al., 2001, 2004), letter identification (Shaywitz et al., 2004) and detection of an unrelated probe in between stimuli (Vinckier et al., 2007). These tasks vary considerably in their attentional demands, ranging from minimal (e.g., passive viewing) to substantial (e.g., reading aloud). Furthermore, some tasks focus attention toward the stimulus as a whole (e.g., word reading), whereas other tasks focus attention away from the stimulus as a whole (e.g., detecting hash marks between letters, letter identification, letter height detection). Studies of word perception have shown that tasks diverting attention away from the word as a whole radically alter the processing of a word, such as elimination of the word superiority effect or repetition priming for words (Hayman & Jacoby, 1989). Thus, diverting attention may affect brain activation patterns as well.

A few neuroimaging studies also suggest that manipulating attention and task will have an effect on the VWFA's activation patterns. One study found that the VWFA activated more for words than pictures in a color naming task, but the difference between words and pictures decreased when participants performed a categorization task (Starrfelt & Gerlach, 2007). Another study found that VWFA response to pseudohomophones differed depending on whether the participant was doing a phonological or orthographic lexical decision task (Twomey et al., 2011). A third study found numerous regions (including a cluster in the left posterior temporal area, close to VWFA coordinates) that responded to words over consonant strings under attended conditions, but did not differentiate the two under conditions of inattention (Rees, Russell, Frith, & Driver, 1999). An EEG study using the same paradigm found an N170 effect (thought to reflect orthographic processing in the posterior fusiform regions(Dehaene et al., 2001; McCandliss et al., 2003)) for words compared to nonwords under attended but not unattended conditions (Ruz, Wolmetz, Tudela, & McCandliss, 2005). Therefore, what appears to be contradictions among studies in relation to stimulus selectivity may, instead, reflect variable interactions between attentional task demands and stimulus types.

The manipulations of attention in prior studies were severe, with tasks and instructions that varied greatly between conditions. Such a severe manipulation of attention is informative about the limits of visual processing of letter strings, but leaves open the question about whether modest variation of attention that occurs in most studies of the VWFA and perhaps during reading also alter the pattern of stimulus specificity in the VWFA. In the present study, we examined whether a subtle manipulation of attention fundamentally alters stimulus-specific activation in the VWFA. If such a subtle manipulation does alter the pattern of activation in the VWFA, then the variation of attention across studies (e.g., active tasks versus passive viewing) may have strong influences on the outcomes of those studies. More generally, such a finding would underscore the importance of attention in the stimulus selectivity of the VWFA,

For each participant, we identified a functional VWFA as a region of interest (ROI) in individual participants in an independent scan (words vs. faces, scenes, and false font). Then we presented words, pseudowords, and consonant strings under two conditions of spatial attention, based on attentional cueing paradigms from Posner (e.g., Posner, 1980), to direct spatial attention toward or away from a letter string. By manipulating both string type and attention, we tested whether there is an interaction between attention and VWFA stimulus selectivity. A pre-stimulus spatial cue drew attention to one of two nearby locations, and the target stimulus then appeared in the cued or uncued location on an equal number of trials. Participants judged whether the stimulus appeared in one or the other location. Thus, the stimuli were easily visible under all conditions. We hypothesized that if attention and stimulus selectivity interact in the VWFA, then the VWFA would exhibit different patterns of stimulus selectivity in the VWFA across the two attention conditions.

Methods

Participants

Twenty-five right-handed monolingual English speakers (9 males, 18-29 years old, mean age 22.4) with no history of reading difficulty were recruited from the university and surrounding community. Informed consent for participation in the study, approved by the MIT Institutional Review Board was obtained from all participants.

Participants were characterized on four measures of reading skill to make certain that they had no reading impairment. Untimed reading ability was assessed with the “Word Identification” and “Word Attack” tests from the Woodcock Reading Mastery Test-Revised, NU (WRMT-R)(Woodcock, 1998); timed reading ability was assessed with the “Sight Word Efficiency” and “Phonemic Decoding Efficiency” tests from the Test of Word Reading Efficiency (TOWRE) (Torgesen, Wagner, & Rashotte, 1999). Participants were excluded if they scored more than one standard deviation (< 85) below the mean on any of these standardized measures of reading so that all included participants had normal reading abilities.

One participant was excluded from further analysis based on reading measures (TOWRE Sight Word Efficiency standard score < 85). Two other participants were excluded from analysis due to software failure. Reading scores from the remaining 23 participants are summarized in Table 1.

Test	Mean Standard Score (All participants)	Range (All participants)	Mean Standard Score (Participants in ROI analysis)	Range (Participants in ROI analysis)
Word ID	109 (9)	98 -125	110 (8)	98-124
Word Attack	112 (13)	92 – 147	104 (13)	98-134
Sight Word Efficiency	107 (8)	92 – 113	107 (9)	92-113
Phonemic Decoding Efficiency	107 (9)	91 – 120	109 (8)	94-120

Table 1: Reading Scores for All Participants

Materials

Localizer

Stimuli for the localizer consisted of words, faces, scenes, and false-font strings (252 each). Words and letters strings were displayed in uppercase Courier New font. The mean frequency per million was 40.8 per million as listed in the English Lexicon Project (Balota et al., 2007), and the mean imageability was 5.95 on a scale of 0 to 7 as listed in the N-Watch database (Davis, 2005). The average number of letters was 4.56 (range: 4-5).

We created a false-font by rearranging individual letters to form a false-font counterpart (Figure 1), and false-font strings were created by replacing each letter in a word with its equivalent false-font letter. The faces and scenes were photographs of faces and natural scenes that were originally black and white, but tinted red and green with Photoshop. Words and false-fonts were presented in red and green font. Stimuli in each condition were evenly divided between the two colors. Faces and scenes subtended approximately 9 degrees of visual angle. Words and false fonts subtended approximately 1 degree.

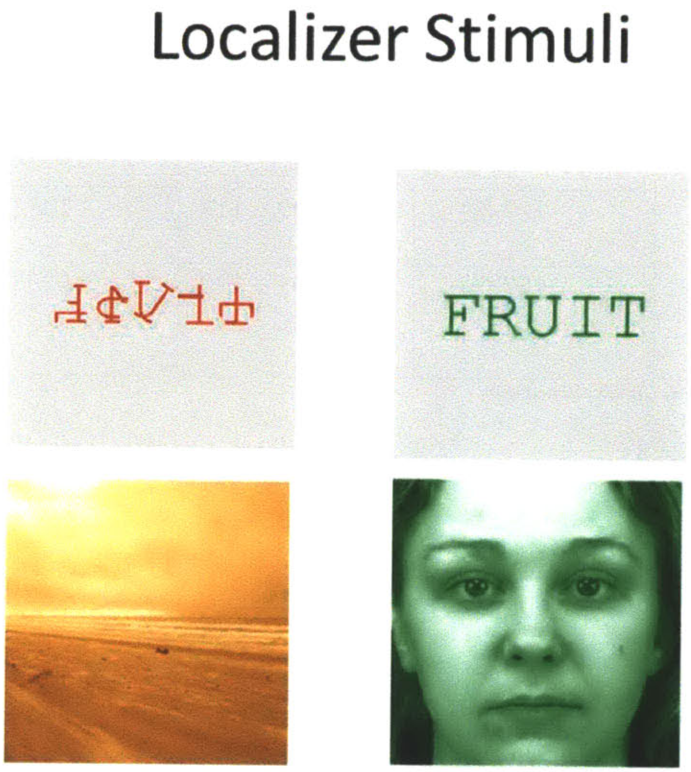


Figure 1 Localizer Stimuli

Attentional Cueing Task

Stimuli for the attentional cueing task consisted of words, pseudowords, and consonant strings (Table 2). Words and pseudowords were equated for letter length, syllable length, mean letter frequency, mean bigram frequency, mean trigram frequency, and proportion of repeated letters per letter string. Consonant strings, due to the absence of vowels, differed by most of these measures. There were no repeated words between the localizer and the attentional cueing task.

	Frequency	Imageability	# Syll	Mean Letter frequency	Mean bigram Freq.	Trigram Freq.	Prop. repeated letters
Words	5.00 (4.77)	523 (68)	2.0 (.42)	6.11 (.94)	2.6(.35)	1.3 (.51)	0.45
Pseudowords			2.0 (.54)	6.26 (1.1)	2.7 (.24)	1.5 (.43)	0.47
Consonants				4.75 (78)*	.63 (.44)*	0.03 (0.12)*	0*

Table 2 Stimulus Characteristics *= Significantly different from Word and Pseudoword value (p<.05)

Procedure

Localizer

Each stimulus appeared for 100 ms, followed by 566 ms of fixation. We used a low-level color detection task and rapid presentation time to discourage participants from approaching different stimulus categories with different strategies. Participants were instructed to press the response button if they saw a green stimulus. Each block had 18 trials and was 12 s long. The localizer task consisted of two runs of 266 seconds each. Each run had 7 blocks per condition for a total of 28 blocks per run, plus 9 fixation blocks. Stimuli were presented on a rear projection screen on a gray background via PsychToolBox software (Brainard, 1997; Kleiner et al., 2007).

Attentional Cueing Task

The attention task had an event-related design and is diagrammed in Figure 2. In each trial, participants were presented with 500 ms of a fixation cross, followed by an 83 ms box cue that appeared either above or below the fixation cross. Participants were told that the box cue was irrelevant to the task and to disregard it. After that, a letter string (word, pseudoword, or consonant string) appeared for 67 ms either above or below the fixation cross. The distance from the fixation cross to the top edge of presented strings subtended about 1 degree of visual angle. The total stimulus presentation time was kept at 150 ms to minimize the possibility of the participant making a saccade to the stimulus (see Bourne, 2006 for review). Participants pressed one button if the string appeared above the fixation and another button if the string appeared below. Letter string position was 50% above and 50% below for all conditions (and thus unpredicted by the box cue). All button presses were done with the participant's left-hand to minimize motor related activation in the left hemisphere. There were 75 trials per condition, and the total experiment consisted of three 350s runs with 175 trials each. Order of trials was optimized with Optseq (http://www.freesurfer.net/optseq/).

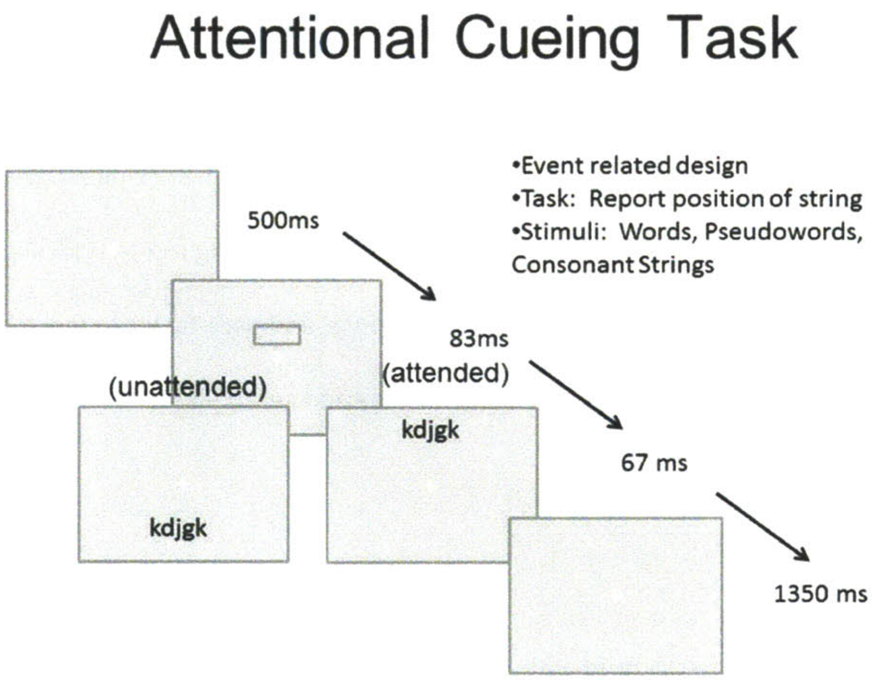


Figure 2 Attentional Cueing Task

Scanning Protocol

FMRI scanning took place at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research at MIT. Imaging was performed using a Siemens 3T MAGNETOM Trio, A Tim System, (Siemens Medical Solutions, Erlangen, Germany) and a prototype custom made 32Ch receive –only phased array head coil. High-resolution structural whole-brain images were acquired using a T1-weighted anatomical scan (128 slices per slab; 256 base resolution ; 256 mm FOV; 1.33mm slice thickness; TR=2530ms; TI=1100ms; TE=3.39ms; flip angle=7°; interleaved acquisition).

Functional data were collected using a gradient echo T2*-weighted EPI sequence sensitive to the BOLD contrast (32 slices, 3 mm slice thickness, voxel size 3 x 3 x 3mm, 64 base resolution, 192mm field-of-view, TR = 2s, TE = 30ms, flip angle=90°, bandwidth=2298 Hz/Px, echo spacing=0.5ms; interleaved acquisition). Slices were placed at an oblique orientation parallel to the AC-PC line. We made sure that the lowest part of the occipital lobe and the bottom part of the temporal lobe in the left hemisphere (including the temporal pole) were covered. The uppermost part of the cortex in the frontal and parietal lobes were included, and occasionally the dorsal-most part of the motor cortex and cerebellum.

Statistical Analyses

The analysis was performed with SPM8, FreeSurfer, Artifact Rejection Toolbox (ART) and Advanced Normalization Tools (ANTS) using Nipype and bash scripts for workflow design and execution. Functional images were realigned to the mean image and smoothed with a 6mm FWHM Gaussian kernel. The functional image co-registration to the 3D anatomical was performed in Freesurfer using a surface based registration algorithm (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Structural and functional images were normalized to the Montreal Neurological Institute (MNI) space using ANTS (Klein et al., 2009). Data was high pass filtered with 128/s cutoff. In the first level analysis, each condition was convolved with a canonical HRF. A one-lag autoregression (AR(1)) model was used to correct for serial (i.e., temporal) autocorrelations. The ART toolbox was used to detect motion outliers. Timepoints whose position deviated from the previous by more than 1 mm, or whose average signal intensity deviated from the series average by more than 3 standard deviations, were added to the model as nuisance regressors.

Whole brain random-effects analyses were performed by entering the SPM contrast images aligned to the subject specific ANTS normalized brain from the first level analysis into a second-level analysis of covariance. The ANTS normalization resampled the functional images to a voxel size of $1mm^3$. Analyses were performed at a voxel-wise threshold of $p<.05$, with FDR cluster correction of $p<.05$ to control for multiple comparisons.

Regions of interest (ROIs)

We defined ROIs by taking the closest cluster for the “words > faces, scenes, and false fonts” contrast in each subject individually at a threshold of $p<.001$ uncorrected. We selected the closest cluster to the peak of visual word form area as identified by Cohen et al. (2002) ((-42,-57,-15) Tal, converted to MNI (-42,-58,-21)]. Because activation varied greatly between individuals and sometimes consisted of multiple connected clusters, the ROI was masked by the left fusiform gyrus as defined by the Talairach atlas(Talairach & Tournoux, 1988). The location and extent of the regions of interest are visualized in Figure 3. Six participants were excluded from ROI analysis because there was no activation in the left fusiform region. We extracted the average beta values for each condition in the attentional cueing task with in-house software.

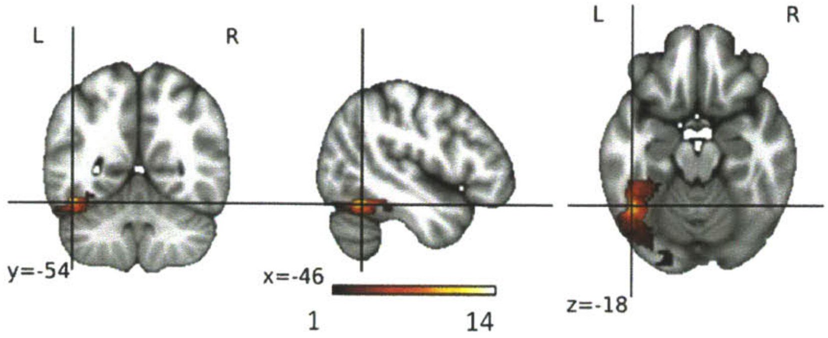


Figure 3 Composite Image Showing Distribution of Participant ROIs

Results

Behavioral

Localizer

Participants averaged 96% accuracy (SD=3%). Mauchly's test indicated that the assumption of sphericity had been violated for accuracy (chi-square = 12.07, p =.03), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon =.75). There were no trends of a main effect of condition on accuracy [F(2,24, 47.00) = 0.38, p=.71].

Average reaction time for correct trials was 352 ms (SD = 28ms), and there was a main effect of condition on reaction time [F(3, 63) = 41.56, p<.001]. The average reaction time for words (363 ms, SD = 32ms) was slightly longer than for faces (341 ms, SD = 27ms) [t(21) = 9.95];

p<.001] and scenes (345 ms, SD = 28ms) [t(21) = 9.14; p<.001]. There was no reaction time difference between words and false fonts (360ms, SD = 27ms) [t(21) = 1.66; p =.11).

Attentional Cueing Task

Accuracy*:* A 3 (string type: words, pseudowords, consonant strings) x 2 (attention: attended, unattended) ANOVA revealed a main effect of attention [F(1, 21) = 5.8 , p<.025] with accuracy being 1.26% lower for the unattended conditions (Table 3). There was no main effect of string type [F(2,42) < 1]. The assumption of sphericity had been violated for the string type x attention interaction (chi-square = 6.18, p =.05). Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon =.79). There was no significant interaction between the two factors [F(1.67, 1.58) = , p=.16].

Reaction time: A 3x2 ANOVA revealed a main effect of attention [F(1, 21) = 216.20, p<.001] with responses being on average 37 ms faster in the attended condition than the unattended condition (Table 4). There was no main effect of string type [F(2,42) <1], and no significant interaction[F(2,42) = 1.18, p=.32].

	Words	**Pseudowords**	**Consonants**
Attended	92.8 (6.5)	93.8(8.0)	92.4 (9.2)
Unattended	91.7 (8.0)	91.3 (7.8)	92.4 (7.2)

Table 3 Mean percentage accuracy and standard deviation (in parentheses) for in-scanner task performance. Accuracy was significantly higher for the attended condition.

	Words	Pseudowords	Consonants
Attended	425 (62)	421 (60)	468 (59)
Unattended	466 (61)	469 (65)	445 (59)

Table 4 Mean reaction time (ms) and standard deviation for in-scanner task performance. Reaction time was significantly faster in the attended condition.

ROI Analysis

We examined activation in the *a priori* defined VWFA (Figure 4) in a 3x2 ANOVA. There was no main effect of attention [F(1, 15) = 0 .78, p=.39], a main effect of string type [F(2, 30) = 3.94 , p= .03], and, critically a significant interaction between attention and string type (F(1.35, 20.27) = 3.95, p=.05). The assumption of sphericity had been violated for the string type x attention interaction (chi-square = 9.15, p =.01), so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon =.68).

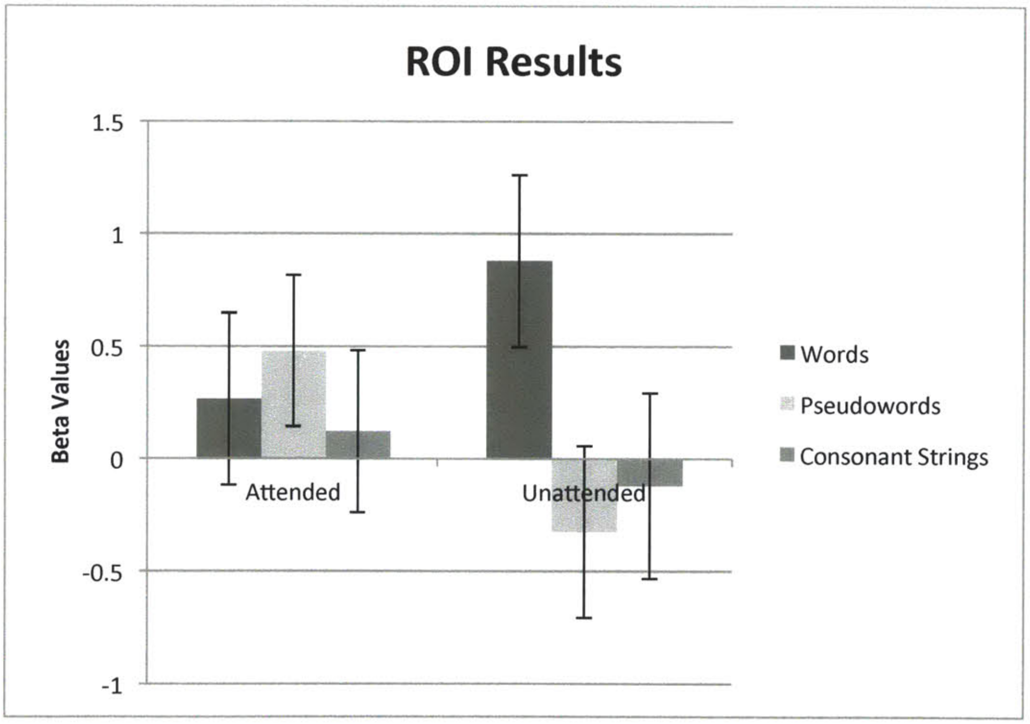


Figure 4 ROI Results. There were no differences between words and other stimuli in the attended condition. In the unattended condition, activation was great to words than to pseudowords and consonant strings.

Simple test effects on the interaction reflected an effect of string type in the unattended condition, (F(2,30) = 6.03, p=.006), which reflected that activation was greater to words than to pseudowords (t(15)=2.77, p=.007) and consonant strings (t(15) = 2.56, p=.01), whereas there was no difference between pseudowords and consonant strings (t(15) = .78, p=.23). In contrast, there was no effect of string type in the attended condition, (F(2,30) = 0.73, p=.40).

The type of string x attention interaction also reflected that activation for words trended to be less in the attended condition than the unattended condition [t(15)=1.67, p=.059]. Conversely, activation for pseudowords was greater in the attended than unattended condition [t(15) = 2.70, p = .008]. There was no effect of attention on activation for consonant strings [t(15) = .71 , p=.49].

One tailed T tests showed that activation to words in the unattended condition was reliably above baseline [t(15) = 2.04, p=.03]. All other conditions were not significantly from baseline, though there was a trend for the aseudoword attended condition [t(15) = 1.4, p=.10].

Whole Brain Analysis

Whole brain clusters are listed in Table 5 **Error! Reference source not found.** There was no above threshold activation for the Words Attended > Words Unattended contrast. For the opposite contrast (Words Unattended > Words Attended), there was extensive activation bilaterally along the length of the temporal lobe, as well as in the left superior and inferior parietal lobule (Figure 5). For the pseudowords attended > pseudowords unattended contrast, participants showed activation in bilateral occipital lobe as well as right inferior parietal lobule and bilateral middle and superior frontal gyrus (Figure 6). For consonant strings, there were no differences between the attended and unattended condition in either direction.

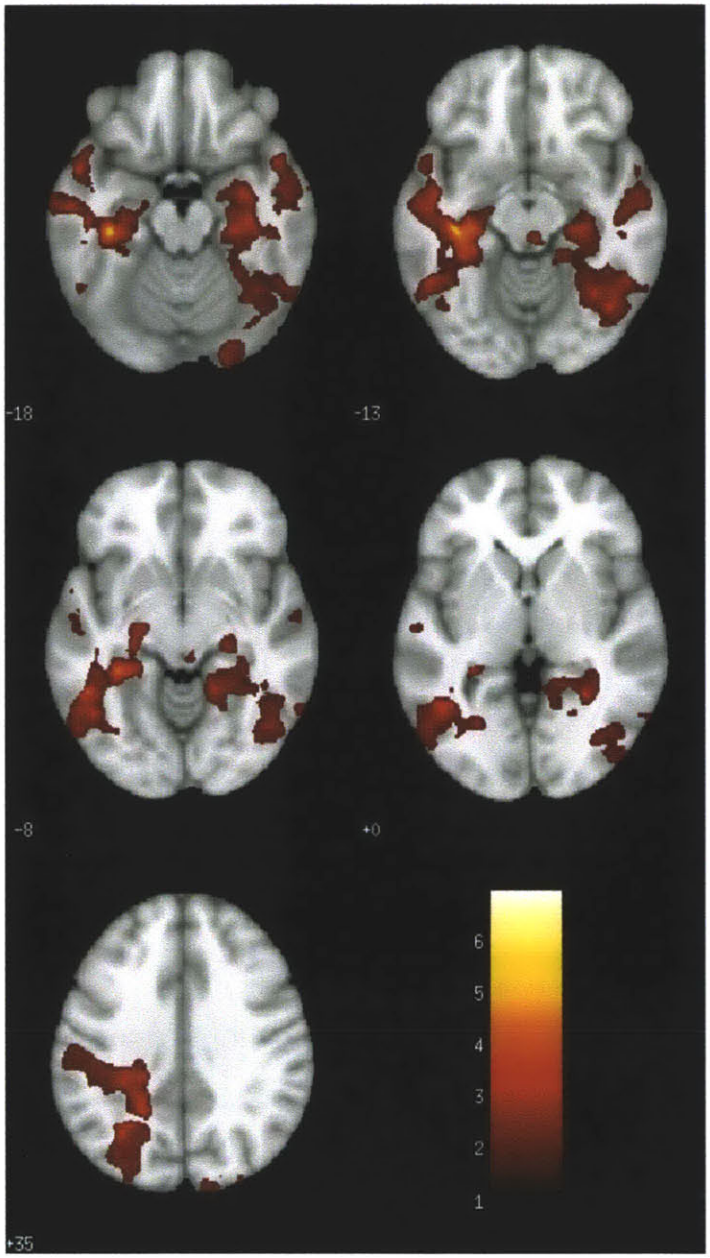


Figure 5 Word Unattended vs. Word Attended

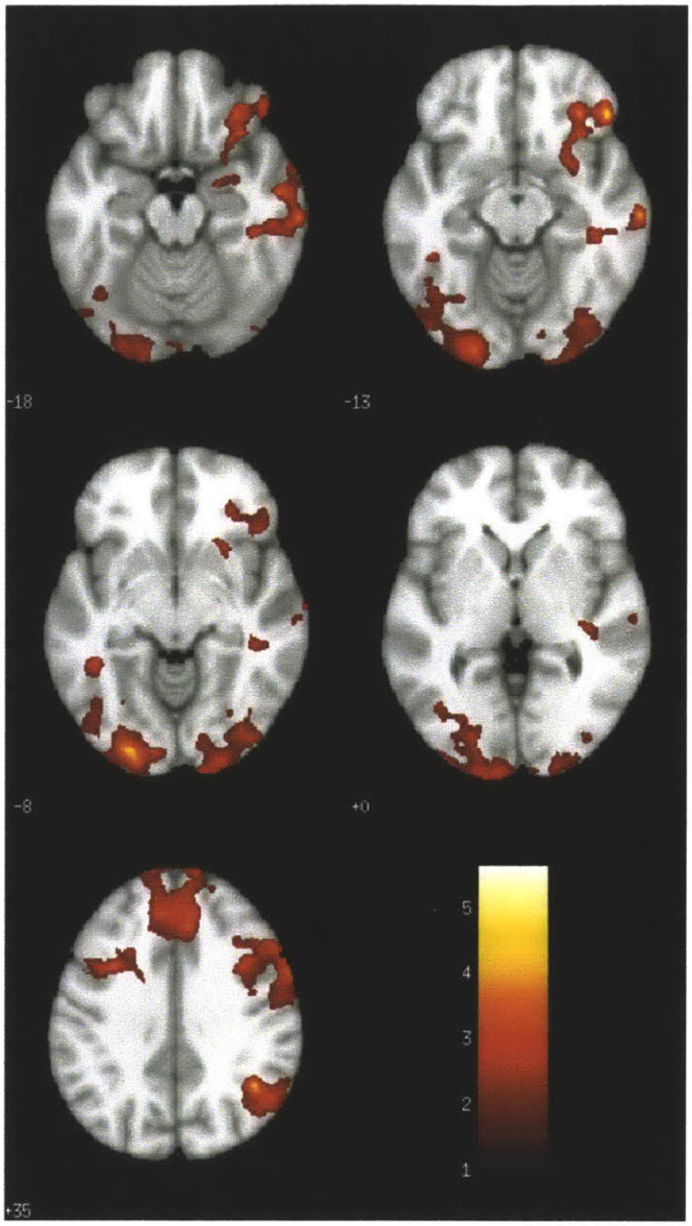


Figure 6 Pseudoword Attended vs. Unattended

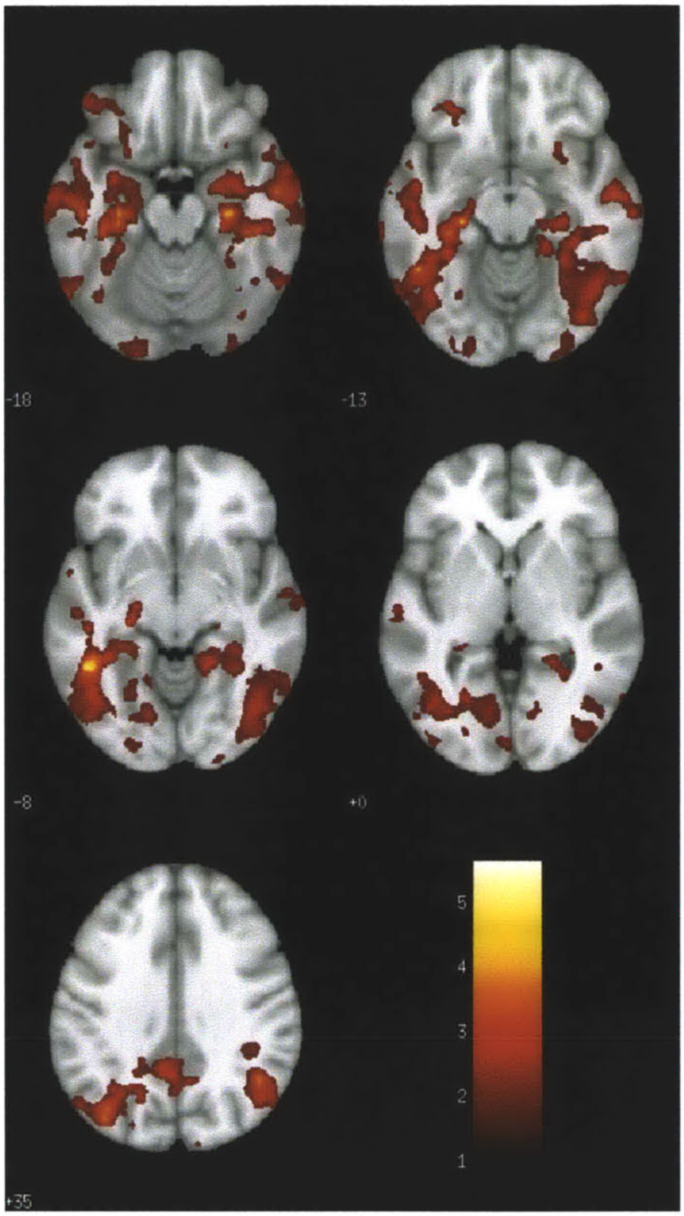


Figure 7 Unattended (Words > Pseudowords) > Attended (Words > Pseudowords)

We also looked for regions that had a greater difference between words and pseudowords in the unattended condition compared to the attended condition (Unattended (Words > Pseudowords) > Attended (Words > Pseudowords)). These areas include bilateral fusiform gyrus, bilateral temporal lobe, and left inferior frontal gyrus (Figure 7).

cluster	cluster	peak	peak				
p(FDR-cor)	equivk	T	equivZ	x	y	z	Location (aal)
Words Attended > Words Unattended							
No Clusters							
Words Unattended > Words Attended							
0	64309	6.98	4.97	-37	-27	-16	Temporal_Inf_L
		4.68	3.83	-32	-40	-6	ParaHippocampal_L
		4.27	3.58	-29	-25	-13	Hippocampus_L
0.021	31671	3.67	3.19	35	-21	-20	ParaHippocampal_R
		3.5	3.07	27	-25	-15	ParaHippocampal_R
		3.25	2.89	42	-66	-13	Occipital_Inf_R
Pseudowords Attended > Pseudowords Unattended							
0	58332	5.63	4.35	14	31	62	Frontal_Sup_Medial_R
		5.55	4.31	-12	30	62	Frontal_Sup_L
		4.73	3.86	30	29	57	undefined
0.013	23919	4.57	3.77	-24	-91	-8	Occipital_Inf_L
		3.3	2.93	-44	-44	-10	undefined
		2.95	2.67	-30	-84	8	Occipital_Mid_L
0.013	25218	4.49	3.72	46	-53	45	Parietal_Inf_R
		4.04	3.44	43	-54	34	Angular_R
		3.63	3.16	56	-59	42	Parietal_Inf_R
0.013	24688	4.37	3.64	48	33	-14	Frontal_Inf_Orb_R
		4.06	3.45	22	1	-30	Parahippocampal_R
		4.05	3.44	66	-24	-17	Temporal_Mid_R
Pseudowords Unattended > Pseudowords Attended							
No clusters							
Consonants Attended > Consonants Unattended							
No clusters							
Words Attended > Pseudowords Attended							
0.001	43744	5.47	4.27	-10	-3	-2	undefined
		4.74	3.87	22	-5	1	Pallidum_R
		4.53	3.74	25	-49	-37	undefined
Pseudowords Attended > Words Attended							
No clusters							
Words Attended > Consonants Attended							

0	82196	4.4	3.66	17	-33	-24	Cerebelum_4_5_R
		4.21	3.55	17	2	-4	Pallidum_r
		4.17	3.52	-9	-3	-3	undefined
Consonants Attended > Words Attended							
No clusters							
Words Unattended > Pseudowords Unattended							
0	232940	4.85	3.93	-35	-32	-15	Temporal_Inf_L
		4.64	3.81	34	20	-29	Temporal_Pole_Sup_R
		4.47	3.71	-34	-18	-35	Fusiform_L
Pseudowords Unattended > Words Unattended							
No clusters							
Words Unattended > Consonants Unattended							
0	132796	4.43	3.68	49	-53	-12	Temporal_Inf_R
		4.19	3.53	34	-22	-19	ParaHippocampal_R
		4.1	3.47	40	-41	35	undefined
0	48742	3.39	2.99	-2	-88	5	Calcarine
		3.27	2.9	-42	-35	41	Parietal_Inf_L
		3.25	2.89	-24	-70	47	Parietal_Sup_L
Consonants Unattended > Words Unattended							
No clusters							
Pseudowords Unattended > Consonants Unattended							
No clusters							
Consonants Unattended > Pseudowords Unattended							
0	48708	4.67	3.83	3	-11	11	Thalamus_R
		4.59	3.78	58	-66	30	undefined
		4.24	3.57	-5	-41	7	Cingulum_Post_L
Unattended (Words > Pseudowords) > Attended (Words > Pseudowords)							
0	89504	5.63	4.35	-47	-49	-10	Temporal_Inf_L
		4.75	3.87	-30	-22	-16	Hippocampus_L
		3.99	3.4	-35	-69	28	Occipital_Mid_L
0.001	51499	4.29	3.6	28	-21	-19	ParaHippocampal_R
		3.81	3.28	45	-56	34	Angular_R
		3.63	3.16	55	-10	-17	Temporal_Mid_R

Table 5 Whole Brain Clusters

Discussion

A small manipulation of spatial attention fundamentally altered the pattern of stimulus response in the putative VWFA and also across many other brain regions. Attention was manipulated with a spatial cuing task that drew attention towards or away from the location where a letter string appeared. The manipulation of spatial attention was validated behaviorally with small but significant gains in accuracy and speed of response for letter strings appearing in the expected location, and this occurred irrespective of the letter string type. More importantly, this modest manipulation of attention altered the pattern of VWFA stimulus selectivity for different string types. In the attended condition, there was no difference in VWFA response to words, pseudowords, and consonant strings. In the unattended condition, however, words showed greater activation than pseudowords and consonant strings. Attention towards stimulus location had three different influences on activation depending on letter-string type: it decreased activation for words, increased activation for pseudowords, and did not alter activation for consonant strings. Thus, an interaction between top-down allocation of spatial attention and bottom-up stimulus properties of print fundamentally altered the stimulus selectivity of the VWFA.

A subtle manipulation of spatial attention yielded opposite effects for words and pseudowords. Reduced activation for words in the attended relative to unattended condition may reflect the more efficient processing for words in the attended location. Indeed, familiarity with a word form has been found to result in decreased VWFA activation (Kronbichler et al., 2004; Kuo et al., 2003) (but see Carreiras, Mechelli, & Price, 2006; Chee, Hon, Caplan, Lee, & Goh, 2002; Chee, Venkatraman, Westphal, & Siong, 2003; Fiebach, Friederici, Müller, & Cramon, 2002). Also, training on unfamiliar scripts has been found to decrease fusiform activation (Xue & Poldrack, 2007). The whole-brain results both complemented and extended the VWFA findings. In the case of words, several other clusters along the length of the temporal lobe also exhibited greater activation for the unattended condition, suggesting more effortful processing of unattended words within the language network beyond the left fusiform.

Another related explanation for the increased activation to words in the unattended condition may be that of attentional capture. Because words inherently carry meaning, they may capture attention even when presented in an unattended location, thus increasing word related activation. This possibility is supported by the extensive parietal activation in the unattended word condition, as the parietal lobe has been reported to be involved in the shifting and control of attention (Gitelman et al., 1999; Peelen, Heslenfeld, & Theeuwes, 2004; Olivier Simon et al., 2004).

In contrast to words, there was a trend toward enhanced activation for pseudowords in the attended relative to unattended condition. Given that participants simply had to note the location of the letter strings, they were not obliged to linguistically analyze the pseudoword strings. It may be the case, however, that the greater attention to the pseudowords encouraged some degree of linguistic analysis, such as noting sublexical constituents of the pseudowords that make these stimuli pronounceable. This greater language processing resulted in greater activation. Conversely, reduced attention to pseudowords may have resulted in those letter strings being treated similarly to non-pronounceable consonant strings. Indeed, the absence of any attentional influence on nonpronounceable consonant strings supports that idea that word-like properties of the pseudowords mediated the influence of attention on VWFA activation. It is worth noting that the brain network activated for the pseudowords attended > pseudowords unattended contrast was different from the network activated for the words unattended > words attended contrast. Whereas manipulation of attention to words altered activations in brain regions associated with visual language in temporal and parietal regions, manipulation of attention to pseudowords altered activations in lower level visual regions and several areas not often reported to be involved language processing, including a some right lateralized activations. This suggests that attention alone was not sufficient for pseudowords to be processed fully as words.

In the region of interest analysis, activation to words in the attended condition was not significantly above baseline (although activation in the unattended was reliably above baseline). This may be due to a combination of three factors. First, the baseline condition was not a blank screen, but a fixation cross, which is a symbol that the VWFA responds to. Therefore, the VWFA may have been activated in the baseline condition. Second, low activation for attended words may also be due in part to the ROI selection criteria. Using the left fusiform as a mask may have excluded some temporal-lobe VWFA activation while including early visual regions that had responded to low-level differences in the localizer rather than the higher-level properties of letter strings. Finally, the contrast we used in defining the ROI was words compared to faces, scenes, and false fonts. The inclusion of the false fonts as a contrast stimulus may have excluded some portions of the VWFA, since false fonts have been shown in some cases to activate the VWFA more than letters.

The strong interaction between attention and letter-string type in the brain is all the more salient because of the minimal behavioral demands of the task. The spatial attention manipulation resulted in a mere 37 msec difference in response time and 1.26% difference in accuracy between attended and unattended conditions. Furthermore, the behavioral response for the stimuli was simply categorizing whether the stimulus appeared above or below the central fixation. Therefore, there was no influence of stimulus type on speed or accuracy of response, and no behavioral interaction between attention and stimulus type. Activation differences, therefore, cannot be accounted for by different behavioral demands for processing words, pseudowords, or consonant strings. Furthermore, despite the words and pseudowords being carefully matched for many characteristics (Table 2), the attentional manipulation resulted in opposite patterns of activation for words and pseudowords in the VWFA and across many other brain regions.

Previous EEG studies have also demonstrated that attentional manipulation may affect early stages of word processing. Most studies of attentional modulation have focused on the N400, a component related to semantic processing (Bentin, Kutas, & Hillyard, 1993, 1995; Cristescu & Nobre, 2008; McCarthy & Nobre, 1993), but some studies have found effects of attentional modulation on the N200, which is thought to originate from the left fusiform. Attending to orthography resulted in an enhanced N200 component over the left posterior parietal region in one study (Ruz & Nobre, 2008), and in another study an orthographic task (case matching) resulted in an enhanced N150 compared to phonological or semantic tasks

(Spironelli & Angrilli, 2007). Functional MRI cannot distinguish the time course of attentional effects on letter-string processing, but it can point to the VWFA as one locus of the interaction between attention and stimulus type.

The present findings demonstrate an interaction between attention and VWFA selectivity, but a review of the literature does not reveal a simple principle underlying this interaction. Only a few studies have directly probed attentional effects on VWFA selectivity. Whereas we found equal activation for words and consonant strings in the attended condition and greater activation for words than consonant strings in the unattended condition, Rees et al. (1999) found the opposite in the left posterior temporal region, close to the VWFA coordinates. This discrepancy could be due to several differences between their protocol and ours, including the nature of their attentional manipulation, which involved attending to one of two spatially overlaid images, their task (one-back), or different stimulus presentation times (250ms in the Rees et al. study, compared to 67ms in our paradigm).

A review of other studies involving the left occipital temporal region reveals some hints of a relationship between task and activation pattern. Many experiments that found greater activation for words compared to consonant strings had tasks that did not require actual reading of the letter string – i.e., passive viewing, identifying hashmarks interspersed between stimulus presentations, and ascender detection. It could be argued that in tasks like these, words capture attention by means of their familiarity and semantic content, thus resulting in higher activation. Baker et al (2007) conducted a posthoc comparison between extrastriate selectivity in both a passive viewing task and a one back task. In accordance with that explanation, they found greater activation for words compared to consonant strings in the passive viewing task, but not the one back task. However, other findings do not fit this pattern. Baker et al. also carried out an event-related experiment in which the task was to report the stimulus' direction of motion across the screen. In this case, attention should have favored the words, but Baker et al. found equal response to words and consonant strings. Likewise, Cohen et al., (2003) had also found similar VWFA activation for words compared to consonant strings in a passive viewing task.

In summary, we have demonstrated that subtle attentional influences fundamentally alters the pattern of stimulus selectivity in the VWFA for words, pseudowords, and consonant strings. These findings speak to a view of the VWFA as more than a low level, stimulus driven area, but as an area affected by an interaction between bottom-up and top-down influences. Indeed, the widespread whole-brain differences in activation between the two attentional conditions supports the view that the VWFA difference is associated with many attention-driven top-down processes that modulate stimulus-specific responses in the VWFA.

Chapter 3: Neural Correlates of Letter Reversal in Children and Adults

Introduction

Parents and teachers often observe that young children reverse individual letters when learning to read and write. Such letter reversal occurs for letters that are mirror images of one another, such as *b* and *d,* or letters for which reversals do not exist, such as *k* or *r*. These latter reversals are especially striking because children are so frequently producing letters that they have never observed in school or in books. Here, we used functional magnetic resonance imaging (fMRI) and event related potentials (ERPs) to compare brain activations between children, ages 5-12, and adults as they viewed typical and reversed letters in order to delineate the brain basis of such letter reversals in children.

Letter reversal and mirror writing were once thought to be a hallmark of dyslexia, but evidence for a selective propensity for such reversals in dyslexia is mixed (Lachman & Geyer, 2003; Terepocki, Kruk, & Willows, 2002). Some studies have found that children with dyslexia display more letter reversal errors (Black, 1973; Lachmann & van Leeuwen, 2007; Terepocki et al., 2002; Wolff & Melngailis, 1996), but other studies have found no difference or very little difference between normal-reading and dyslexic children (Corballis, Macadie, Crotty, & Beale, 1985; Grosser & Trzeciak, 1981). Regardless of the unanswered questions regarding dyslexia, it is clear that letter reversal and mirror writing commonly occurs in non-dyslexic beginning readers. Children between the ages three and seven will often spontaneously mirror-write if asked to write their name next to the right-hand margin of a sheet of paper (Cornell, 1985). As children become more skilled at reading, reversal errors decrease. However, facility at reading transformed text (mirror reversed, inverted, or upside down) changes throughout adulthood, suggesting that the encoding of letter orientation continues to develop past childhood (Wolff & Melngailis, 1996).

One hypothesis for the unexplained frequency of letter reversal in children is that learning to read reflects a specialized adaptation of more general object recognition processes that are insensitive to right-left orientation (Dehaene, 2009; Dehaene, Nakamura, et al., 2010). For purposes of object recognition, generalization across different appearances or perspectives may be helpful (e.g., a dog is a dog regardless of whether the dog is facing to the left or the right). For letters in an alphabet, however, specific right-left orientation is often definitional of the letter (e.g., a *b* vs. a *d,* or a *p* vs. a *q*). Thus, if learning to read letters reflects a specialized skill that is adapted from more general object recognition processes, then reading experience is needed to learn to overcome the initial propensity to disregard right-left orientation. The idea that reading experience is needed to overcome orientation insensitivity is supported by the slow development of orientation specificity in children. Furthermore, learned orientation sensitivity for reading may promote orientation sensitivity for objects: Adults who were literate in a language where mirror orientation mattered for letter identity were more likely to reject mirror image *objects* in a matching task than adults who were literate in a language where mirror orientation does not matter for letter identity (Danziger & Pederson, 1998; Pederson, 2003).

Neuroimaging evidence also suggests that writing systems may be a special case for mirror reversal. Repetition priming studies of the visual word form area (VWFA), an area of the left fusiform gyrus shown to be important for reading (L. Cohen et al., 2002; L. Cohen & Dehaene, 2004; McCandliss et al., 2003), have found that the region generalizes between mirror images of objects, but not of words (Dehaene, Nakamura, et al., 2010) or letters (Pegado, Nakamura, Cohen, & Dehaene, 2011). In addition, studies using event-related potentials (ERPs) to examine the time-course of reading have found letter reversals lead to an increased demand in processing in adult readers (Hamm, Johnson, & Corballis, 2004; Núņez-Peņa & Aznar-Casanova, 2009). However these studies focused on later ERP components that likely reflect mental rotation. We would predict that orientation information is important in early stages of the visual processing of letters and words. One study found that orientation of letters influences the amplitudes of early ERP components, including the P1, which is associated with low-level visual features, and the N170, which is associated with categorization/classification processes (Milivojevic, Hamm, & Corballis, 2011) . Both the P1 and N170 have posterior distributions, likely reflecting generators in primary visual cortex and ventral temporal cortices (Allison, Puce, Spencer, & McCarthy, 1999).

There is, however, no evidence as to how letter orientation is processed similarly or dissimilarly in the brains of children and adults. Here, we compared children and adults viewing typical and reversed letters as we recorded fMRI to examine the location and ERPs to examine the time course of differential responses to typical and reversed letters. Because of its known importance in reading, we examined fMRI responses both in the VWFA as an *a priori* region of interest (ROI) identified in each participant in an independent localizer task and also in a whole-brain analysis. In the ERP portion of the study we expected that the P1 and N170 responses should show sensitivity to orientation information about letters, because the P1 is sensitive to low level visual features, important for identifying stimuli, and the N170 is sensitive for stimulus categorization and has been show to change with the acquisition of reading skills (Maurer et al., 2005). Importantly, these components should show differences on the basis of experience with reading.

Materials and Methods

Participants

Participants were right-handed English speaking children and adults with no history of reading difficulty who were recruited from the university and surrounding community. Participants were required to have been exposed to English from birth, and not to have been exposed to any other language before the age of two. Informed consent for participation in the study, approved by the MIT Institutional Review Board was obtained from all participants. Adults were compensated for their participation and children received gift cards to a book store for participating.

fMRI Experiment

From among a larger group (N=76, 37 adults) , inclusion/exclusion criteria applied to ensure that each participant understood and performed the scanner tasks, and that all participants were typically developing for reading and reading-related skills. Children and adults fit the following criteria: 1) For scanner behavioral performance, had an overall accuracy

> 70% and detected over 70% of target stimuli in both a localizer and the letter reversal task; 2) Scored above a 90 standard score on the Woodcock Reading Mastery Tests (WRMT), Test of Word Reading Efficency (TOWRE), above a standard score of 6 on the Elision, Memory for Digits, Nonword Repetition, and Blending Words subtest of the Comprehensive Test of Phonological Processing (CTOPP), and above a standard score of 85 on the Kaufman Brief Intelligence Test (KBIT). All children meeting these criteria were included in the study, and 15 adults were chosen so that the two groups were matched for KBIT score. The final group consisted of 15 children (9 male, mean age 9.5, age range 5-12) and 15 adults (N = 15, 7 male, mean age 22.3, age range 18-26). Behavioral scores are summarized in Table 6.

EEG Experiment

Of the 30 participants included in the fMRI experiment, 12 of the adults (4 males, mean age 22.3, age range: 18-26) and 10 of the children also participated in the EEG portion of the letter-reversal experiment. An additional two children who did not complete the fMRI experiment or were excluded from the fMRI analysis due to excessive motion were included in the EEG experiment for a total of 12 children (9 males, mean age of 9.4, age range: 7-12). The behavioral performance rates were slightly lower for the children in the EEG experiment due to pressing the wrong button on the response pad in some cases, however, all participants were video monitored during the experiment and were observed to be performing the task.

Stimuli

VWFA Localizer

Stimuli consisted of words, drawings of faces, drawings of objects, and meaningless scribbles (196 each). To control for low level visual characteristics (contour structure and spatial frequency), stimuli were constructed with a computer program that reconstructed the images as dot patterns (Figure 8 Localizer Stimuli). Words were nouns ranging from 3 to 8 letters long (avg = 4.6). Average Hyperspace Analogue to Language (HAL) frequency according to the English lexicon project was 27670 (SD = 124497). Statistics for two words, 'yoyo', and 'bagel' were not available and thus were not included in the average. All stimuli were divided into two matched lists: one for the fMRI portion and one for the EEG portion of the experiment. The words in one list were the names of the line drawings presented in the other list, and vice versa. List assignment was counterbalanced between participants. Black and green versions of all stimuli were created for the task (described below). Stimuli were presented in a box that subtended about 4 degrees visual angle.

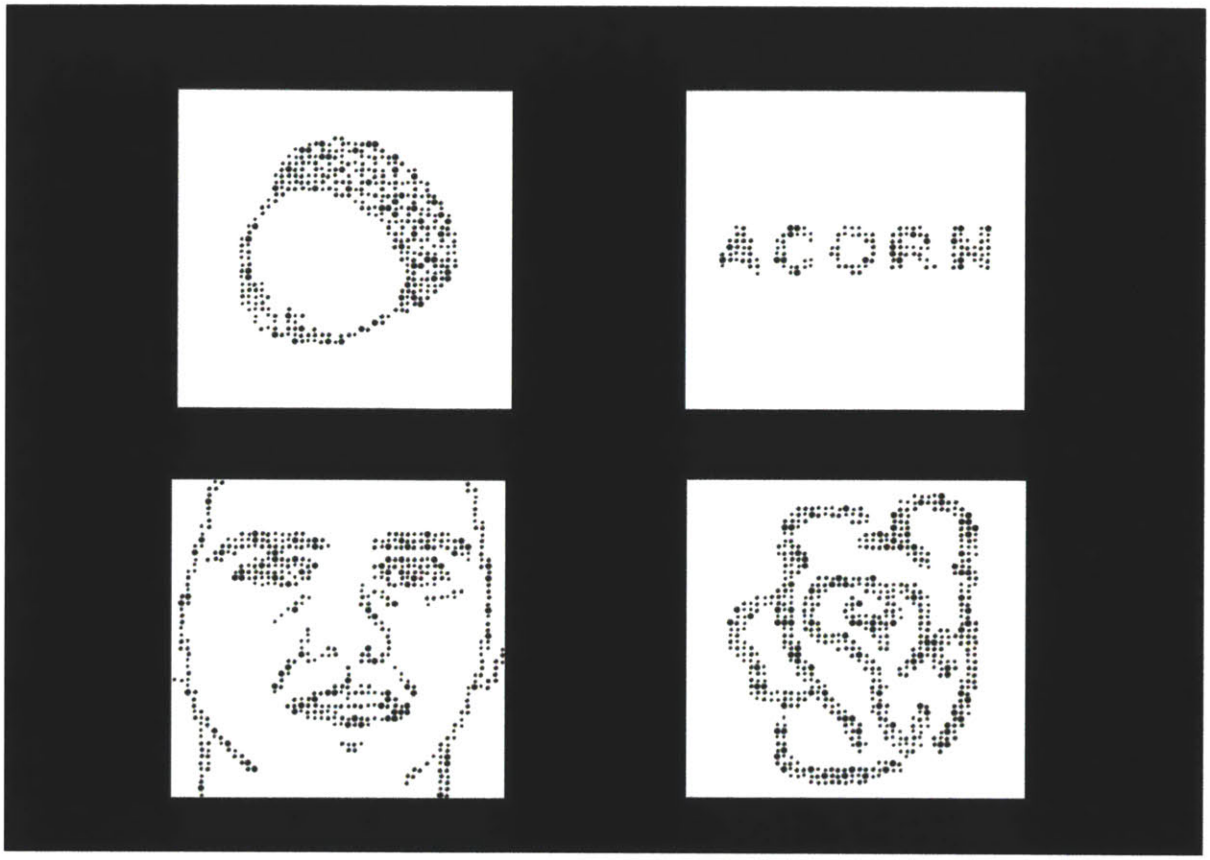


Figure 8 Localizer Stimuli

Letter Reversal Experiment

Stimuli for the letter reversal experiment consisted of lowercase letters, reversed letters, and pictures of chairs (16 each). The letters used where 'a', 'c', 'e', 'f', 'g', 'h', 'j', 'k', 'm', 'n', 'r', 's', 't', 'u', 'y', and 'z'. Black and green versions of all stimuli were created. Stimuli were presented in a box that subtended approximately 4 degrees visual angle. Results from the two letter conditions are reported.

Procedure

fMRI VWFA Localizer

In each trial, participants were presented with a stimulus for 200 ms, followed by 800ms of a blank screen. Stimuli were presented in black and white in a block design fashion, with each block consisting of 14 trials (14s blocks). Participants were instructed to press the response button anytime a stimulus was green, which occurred one or two times per block. Between each block, a cartoon alien flashed on screen for 2 seconds. Because this paradigm was also run on children, participants were told that the experiments were an attempt to teach the alien about color. ERP results for the localizer paradigm are not presented in this paper. Participants were scanned in this experiment for two runs of four minutes and 26 seconds each. In the two runs combined, there were 7 blocks of each condition, plus 6 fixation blocks.

Letter Reversal Task (EEG and fMRI)

As in the localizer task, stimuli in the letter-reversal task were also presented for 200 ms, followed by 800 ms of a blank screen (Figure 9). For the fMRI portion of the study, stimuli were presented in blocks, each consisting of 16 trials, and, like the localizer, there were one or two green stimuli per block. Participants were instructed to press the response button to any green stimulus. As in the localizer, an alien also flashed on the screen for 2 seconds between each block to keep the children engaged in the task. Participants were scanned for two runs of 4 minutes and 12 seconds each. In the two runs combined, there were 7 blocks of each condition.

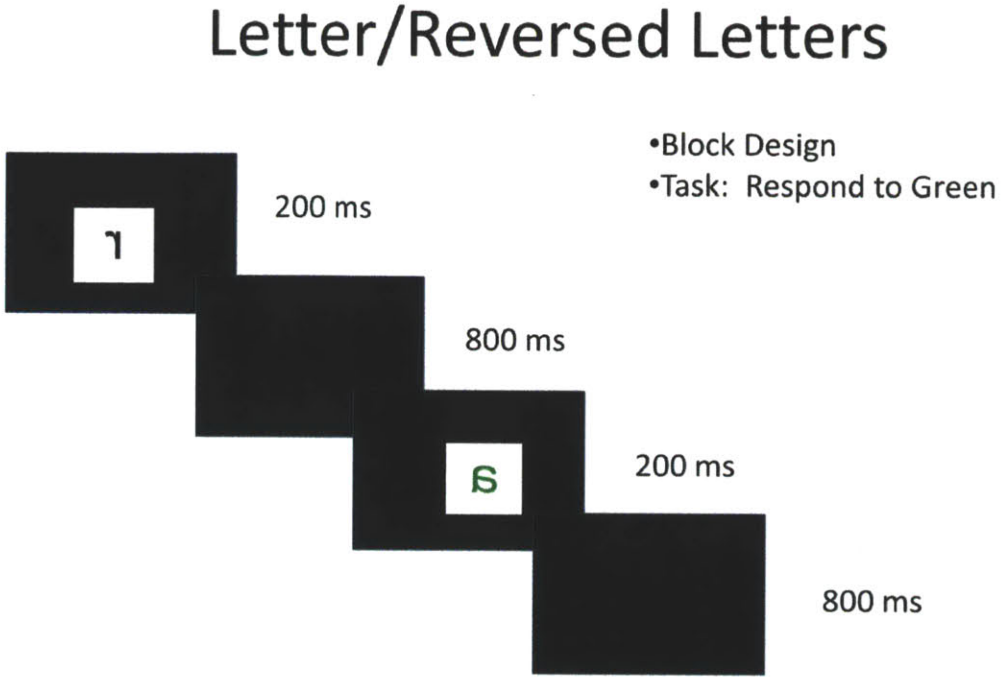


Figure 9 Letter Reversal Task

For the ERP version of the experiment, stimuli were presented for the same duration with the same inter-stimulus interval (ISI) as in the fMRI experiment; however, the stimuli were presented in event-related fashion by pseudorandomizing the order of presentation. Stimulation time was the same as in the fMRI experiment since the amount of fixation time was used a time for blinking in the ERP experiment. The task was exactly the same with the same proportion of green items occurring and the stimuli were broken up into two runs.

FMRI Acquisition and Analysis

FMRI Acquisition

FMRI scanning took place at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research at MIT. Imaging was performed using a Siemens 3T MAGNETOM Trio, A Tim System, (Siemens Medical Solutions, Erlangen, Germany) and a commercial Simens 32 channel head coil. High-resolution structural whole-brain images were acquired using a T1-weighted anatomical scan with motion correction (176 slices per slab; 1 mm isotropic voxel size; TR=2530ms; TE=1.64ms) (Tisdall et al., 2011).

Functional data were collected using a gradient echo T2*-weighted EPI sequence sensitive to the BOLD contrast (2mm isotropic voxel size; TR = 2; TE = 30ms; slices). Slices were placed at an oblique orientation parallel to the AC-PC line. We made sure that the lowest part of the occipital lobe and the bottom part of the temporal lobe in the left hemisphere (including the temporal pole) were covered. The uppermost part of the cortex in the frontal and parietal lobes were covered as well. Slices covered the entire cortex with the exceptions of the dorsal portion of the motor cortex in some participants and usually parts of the cerebellum.

fMRI Analysis: The analysis was performed with SPM8, FreeSurfer, Artifact Rejection Toolbox (ART) and Advanced Normalization Tools (ANTS) using Nipype and bash scripts for workflow design and execution. Functional images were realigned to the mean image and smoothed with a 4mm FWHM Gaussian kernel. The functional image co-registration to the 3D anatomical was performed in Freesurfer using a surface based registration algorithm. Structural and functional images were normalized to the Montreal Neurological Institute (MNI) space using ANTS (Klein et al., 2009). Data was high pass filtered with 128/s cutoff. In the first level analysis, each condition was convolved with a canonical HRF. A one-lag autoregression (AR(1)) model was used to correct for serial (i.e., temporal) autocorrelations. The ART toolbox was used to detect motion outliers. Timepoints whose position deviated from the previous by more than 1 mm, or whose average signal intensity deviated from the series average by more than 3 standard deviations, were added to the model as nuisance regressors. Realignment parameters were also added as nuisance regressors.

Whole brain random-effects analyses were performed by entering the SPM contrast images aligned to the subject specific ANTS normalized brain from the first level analysis into a second-level analysis of covariance, with stimulus correlated motion and number of artifacts as covariates. The ANTS normalization resampled the functional images to a voxel size of 1mm^3. Analyses were performed at a voxel-wise threshold of $p<.01$, with FDR cluster correction of $p<.05$ to control for multiple comparisons.

The words > object contrast at a $p<.001$ uncorrected threshold from the localizer paradigm was used to define a VWFA ROI in each individual's normalized functional scan. The closest cluster to the peak of visual word form area as identified by Cohen et al. (2002) at -42 -57 -15 (Tal, converted to MNI -42 -58-21) was selected. One child and two adults were excluded from this analysis because they did not have a cluster of greater than 5 voxels with a peak within 25 mm of those coordinates.

EEG Experiment Acquisition Parameters and Analysis

EEG Acquisition

EEG was recorded from 61 scalp sites (10-20 system positioning), a vertical eye channel for detecting blinks, a horizontal eye channel to monitor for saccades, and two additional electrodes affixed the mastoid bone. EEG was acquired with the Active Two Biosemi system using active Ag-AgCl electrodes mounted on an elastic cap (Electro-Cap Inc.). All channels were referenced offline to a common average of scalp channels. The EEG was recorded at 512 Hz sampling rate and filtered offline (bandpass 0.1-30 Hz). Trials with blinks, eye movements, and muscle artifact were rejected prior to averaging.

ERP Analysis

For adults and children separately, ERP averages were formed by time-locking to the onset of the letters and reversed letters and averaging across these trials from 100 ms prior to target onset until 700 ms after. We examined three epochs where differences emerged in the ERP waveform across the two groups: the P1 (100-150 ms), the N170 (150-225 ms) and two later epochs (225-325 ms and 325-425 ms). Mean amplitude measurements were taken from posterior electrode sites (P7, P5, P3, P8, P6, P4, PO3, PO4, PO7, PO8, O1, O2) for the P1 and the two later epochs and for the N170 measurements were taken from P7/P8, PO3/PO4, and PO7/PO8). The amplitude was normalized for both groups since children had much larger amplitude ERPs than adults. This normalization was performed by taking the mean amplitude at one electrode site for one condition per subject (score) and subtracting the mean across all subjects in each group from this score and dividing by the standard deviation across all subjects in each group (score – mean/SD) (see Holcomb et al., 1992). This method eliminates main effects of group, but maintains all other main effects and interactions. The normalized mean amplitude from these electrode sites was entered into a repeated measures ANOVA with the within subject factors of letter reversal (reversed or not reversed), electrode site (six levels), and hemisphere (left or right) and the between subject factor of group (adults, children). The Geisser and Greenhouse (1959) correction was applied to all repeated measures having more than one degree of freedom and the corresponding p values are reported. Follow-up analyses were conducted for each group separately with the same within-subject factors listed above on the non-normalized mean amplitudes when a condition x group interaction warranted a follow-up comparison. In addition a peak latency analysis was performed to examine differences in the timing between the groups and between the letter and reversed letter conditions. The peak latency was measured between 125 and 250 ms and on only negative going peaks that were the peak for at least +/- 5 consecutive points.

The non-normalized mean amplitude difference between reversed letters and letters from the ERP experiment at each of the left hemisphere electrodes (P7, PO3, PO7) was included in a correlational analysis with percent signal change difference between reversed letters and letters in the functionally defined VWFA for those participants who had both ERP data as well as a functionally defined VWFA in the fMRI portion of the experiment (N = 17, 10 adults, 7 children).

Results

Behavioral Testing

Standardized reading and fluid intelligence measures for adults and children in the fMRI experiment are listed in Table 6. Adults scored higher than children on all measures, although children had higher standardized (age-adjusted) scores than adults on several reading and reading-related measures.

	KBIT Nonverbal Raw	Kbit Nonverbal SS	Word ID Raw	Word ID SS	Word Attack Raw	Word Attack SS
Adults	41.60(2.01)	114.47 (8.70)	99.87 (3.09)	107.00 (6.07)	38.60 (2.44)	104 (8.90)
Children	34.53 (7.45)*	120.27 (13.54)	78.87 (13.01) **	122.33 (17.04)*	34.60 (5.94)*	120.40 (13.16)**
	TOWRE SWE Raw	TOWRE SWE SS	TOWRE PDE Raw	Towre PDE SS	Elision Raw	Elision SS
Adults	99.93 (5.41)	106.27 (9.004)	57.47 (3.314)	105.53 (8.46)	18.93 (1.10)	10.93(1.10)
Children	74.00 (12.60) **	117.87 (11.38) *	43.13 (9.30)**	119.67 (8.23)**	17.67 (3.18)	13.27(2.19)**
	Memory for Digits Raw	Memory for Digits SS	Nonword Repetition Raw	Nonword Repetition SS	Blending Words Raw	Blending Words SS
Adults	15.80 (6.70)	11.07(3.80)	12.87 (1.96)	9.13 (1.64)	18.40 (1.12)	12.47 (1.13)
Children	13.87(4.53)	11.47(5.04)	10.73 (2.374) *	9.8 (2.11)	14.93 (3.26)**	11.73 (2.25)

Table 6 Behavioral measures for Participants in fMRI Experiment. *p<.05 **p<.001; KBIT = Kaufman Brief Intelligence Test; SS = Standard Score; SWE = Sight Word Extraction; PDE = Phonemic Decoding Efficiency

fMRI Behavioral Performance

Localizer Task

Overall accuracy (measure includes correct rejections), percentage of probes detected, and reaction time for children and adults are listed in Table 7. Mixed model ANOVAs with 4 conditions as a within-subject factor and 2 the age groups a between subject factor were run for each measure.

Adults trended to be more accurate overall (99.7%) than children (98.6%) [F(1,28) = 3.20, p=.09]. The assumption of sphericity was violated for condition (chi-square = 17.10, p = .004), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .77). There was trend toward a main effect of condition [F(2.23,64.26) = 2.56, p=.08], and no condition by group interaction (F(2.23,64.26) = 1.14, p=.33).

Adults detected a significantly higher percentage of probes (98.3%) than children did (93.2%) [F(1,28) = 4.90, p=.04]. The assumption of sphericity was violated for condition (chi-square = 16.40, p = .006), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .74). There was a trend toward a main effect of condition, [F(2.23,62.41) = 1.86, p=.06], and no condition by group interaction (F(2,23) = 1.63, p=.20).

Adults responded faster to targets (488ms) than children (671ms) [F(1,28) = 48.12, p<.001]. The assumption of sphericity was violated for condition (chi-square = 18.50, p = .002), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .70). There was a trend toward a main effect of condition, [F(2.01, 56.19) = 2.65, p=.08], and no condition by group interaction (F(2.01,56.20) = 0.14, p=.70).

% Accuracy	Words	Faces	Objects	Scribbles	Overall
Adults	99.5 (0.8)	99.6 (0.6)	99.7 (0.6)	99.8 (0.4)	99.7 (0.4)
Children	98.2 (2.7)	99.0 (1.8)	98.6 (2.1)	98.7 (2.3)	98.6 (2.1)
% Probes Detected	Words	Faces	Objects	Scribbles	Overall
Adults	97.0 (5.1)	98.5 (3.9)	97.8 (4.6)	98.5 (3.9)	98.3 (2.7)
Children	88.9 (17.3)	98.5 (3.9)	91.9 (12.2)	92.6 (10.0)	93.2 (7.1)
Reaction Time (ms)	Words	Faces	Objects	Scribbles	Overall
Adults	530 (61)	510 (45)	522 (57)	512 (54)	488 (133)
Children	705 (122)	665 (66)	676 (66)	666 (87)	671 (65)

Table 7 Localizer Accuracy and Reaction Time

Letter Reversal Task

Letter reversal task results are in Table 8. Adults were more accurate overall (99.9%) than children (99.5%) [F(1,28) = 4.46 , p=.044]. There was no main effect of condition for accuracy [F(1,28) = .84, p=.37], and no condition by group interaction (F(1,28) = .30, p=.59).

Adults also detected a significantly higher percentage of probes (98.9%) than children did (94.4%) [F(1,28) = 6.3, p=.018]. There was a trend toward higher accuracy in the typical letters condition, [F(1,28) = 2.91, p=.06], and no condition by group interaction (F(1,28) = 2.91, p=.10). Finally, adults responded faster to targets (480ms) than children did (641ms) [F(1,28) = 52.74, p<.001]. There was no main effect of condition for reaction time, [F(1,28) = 2.19, p=.15], and no condition by group interaction (F(1,28) = .04, p=.85).

% Accuracy	**Typical Letters**	**Reversed**	**Overall**
Adults	99.9 (0.3)	99.9 (0.2)	99.9 (0.2)
Children	98.9 (1.7)	99.8 (0.4)	99.5 (0.7)
% Probes Detected	**Typical Letters**	**Reversed**	**Overall**
Adults	98.5 (4)	99.3 (2.3)	98.9 (2.3)
Children	92.6 (12.4)	95.6 (10.1)	94.4 (8.1)
Reaction Time (ms)	**Typical Letters**	**Reversed**	**Overall**
Adults	473 (53)	487 (69)	480 (57)
Children	629 (71)	648 (74)	641 (63)

Table 8 Letter Reversal In Scanner Behavioral Data

Stimulus Correlated Motion and Number of Artifacts

Children averaged 19.27 (SD = 15.88) rejected timepoints (7.24%) as defined in the methods section across both runs of the localizer task, while adults averaged 4.07 (SD=2.92) rejected timepoints (1.5%). Levene's test indicated that the two groups had unequal variances for number of rejected timepoints (F(28) = 19.53; p<.000). An independent samples t test (equal variances not assumed) found children had significantly more rejected timepoints (t(14,94) = 3.65, p =.002). Children (M =.095; SD = .023) and adults (M = .11; SD = .024) did not differ significantly (t(28) = 1.49, p=.15) in the amount of stimulus correlated motion.

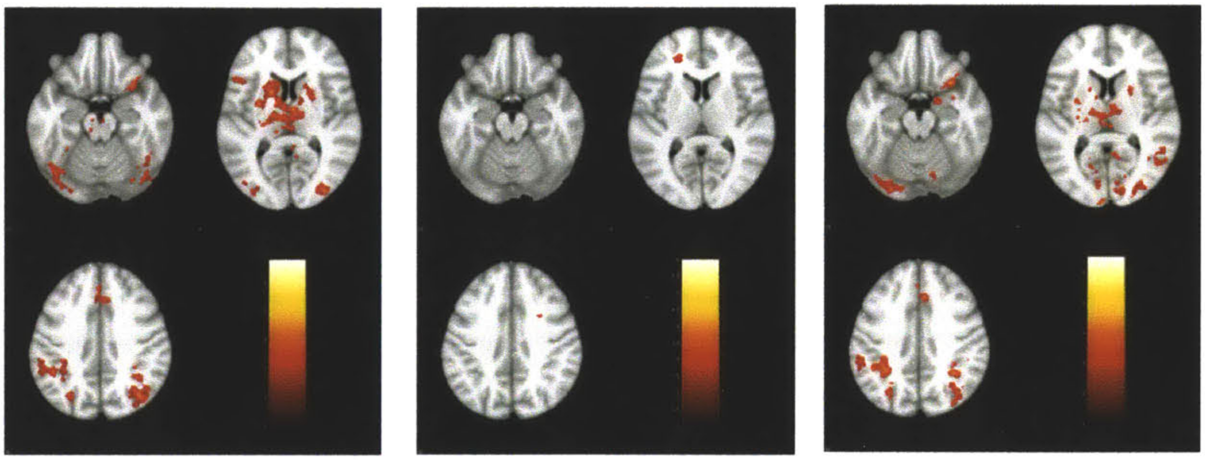
Children averaged 28.60 (SD = 22.33) rejected timepoints (11.35%) as defined in the methods section across both runs of the letter reversal task, while adults averaged 5.67 (SD=5.95) rejected timepoints (5.67%). Levene's test indicated that the two groups had unequal variances for number of rejected timepoints (F(28) = 12.89; p=.001). An independent samples t test (equal variances not assumed) found children had significantly more rejected timepoints (t(15.98) = 3.84; p =.001). Children (M =.087; SD = .019) had significantly less stimulus correlated motion than adults (M = .12; SD = .018) (t(28) = 4.39, p<.000). Because children and adults differed in outliers and stimulus correlated motion, these parameters were added as covariates in the between groups whole brain and ROI analyses.

FMRI Whole Brain Activations

Whole brain results at a voxelwise threshold of .01 with FDR correction of p<.05 are summarized in Table 9. Direct comparison of children and adults showed that adults exhibited significantly greater activation for the reversed > typical letters contrast than children did in multiple regions, including the left ventral visual stream and bilateral parietal cortices (Figure 10). Children did not exhibit greater activation than adults in the reversed > typical letters contrast.

In adults, there was greater activation for reversed than typical letters in multiple regions, including the bilateral ventral visual stream, inferior frontal gyrus, angular gyrus, and inferior parietal lobule; no region exhibited greater activation for typical than reversed letters.

In children, there was greater activation for typical than reversed letters in left inferior parietal lobule, left superior temporal gyrus, and early visual regions (Figure 11). Children showed greater activation for reversed letters than normal letters in the middle frontal gyrus.



Adults **Children** **Adults>Children**

Figure 10 Reversed Letters > Typical Letters

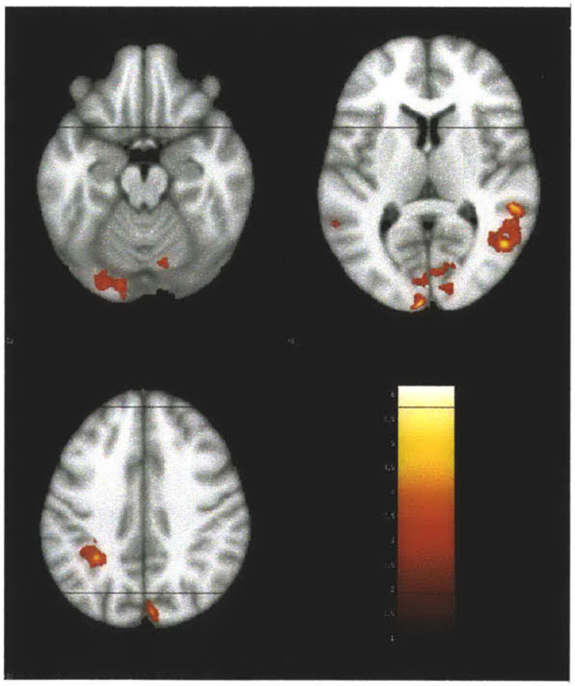


Figure 11 Typical Letters > Reversed Letters in Childre

Normal Letter > Reversed: Children

cluster FDR	size	peak T	x	y	z	Location
0.034	1847	6.18	-31	-48	40	Parietal Lobe
		4.04	-30	-37	44	Parietal Lobe
		3.41	-34	-55	46	Inferior Parietal Lobule
0	4217	5.8	58	-41	10	Superior Temporal Gyrus
		5.14	49	-62	8	Middlemporal Gyrus
		3.81	51	-48	9	Superior Temporal Gyrus
0	6518	5.67	-5	-101	6	Cuneus
		4.87	-10	-99	17	Cuneus
		4.02	-10	-96	-17	Lingual Gyrus
0	8995	4.73	7	-74	19	Precuneus
		4.65	8	-98	19	Cuneus
		4.6	6	-82	38	Precuneus
0.024	2082	4.22	-45	-35	23	Inferior Parietal Lobule
		3.67	-57	-46	16	Superior Temporal Gyrus
		3.35	-54	-38	27	Inferior Parietal Lobule

Reversed> Normal Letters: Adults

cluster FDR	size	peak T	x	y	z	Location
0	8250	6.77	43	-73	-13	Middle Occipital Gyrus
		4.41	36	-86	9	Middle Occipital Gyrus
		4.27	49	-62	-11	Occipital Lobe
0	50298	6.57	-22	4	-7	Extra-Nuclear
		5.87	28	14	-13	Inferior Frontal Gyrus
		5.53	-26	-7	-3	Lentiform Nucleus
0.02	1960	6.03	40	8	32	Inferior Frontal Gyrus
		4.21	44	13	26	Frontal Lobe
		4.04	42	8	18	Frontal Lobe
0	11985	5.31	36	-50	47	Inferior Parietal Lobule
		5.28	37	-68	31	Angular Gyrus
		4.88	38	-77	31	Angular Gyrus
0	6253	5.11	-29	-48	43	Parietal Lobe
		4.84	-44	-45	40	Inferior Parietal Lobule
		3.95	-29	-69	39	Precuneus
0.001	3488	5.05	9	23	33	Cingulate Gyrus
		3.56	1	20	55	Superior Frontal Gyrus
		3.5	-1	35	38	Medial Frontal Gyrus
0.007	2510	4.39	-35	1	54	Middle Frontal Gyrus
		3.82	-23	15	59	Middle Frontal Gyrus
		3.43	-26	7	61	Middle Frontal Gyrus
0.01	2280	3.68	-4	-33	-30	Pons
		3.66	3	-23	-29	Pons
		3.59	8	-31	-29	undefined

Reversed>Normal Letters: Children

cluster FDR	size	peak T	x	y	z	Location
0.039	1932	6.02	29	23	23	Frontal Lobe
		4.27	23	16	28	Frontal Lobe
		3.36	28	9	39	Frontal Lobe
0.039	2003	4.31	-26	40	-1	Middle Frontal Gyrus
		3.93	-22	45	5	Sub-Gyral
		3.79	-15	43	18	Medial Frontal Gyrus

Reversed>Normal:Adults>Children

cluster FDR	size	peak T	x	y	z	Location
0	8252	6.52	-29	-48	42	Parietal Lobe
		4.5	-44	-45	40	Inferior Parietal Lobule
		4.36	-31	-37	45	Parietal Lobe
0	6139	6.33	38	-77	31	Angular Gyrus

		4.78	38	-68	31	Angular Gyrus
		4.48	12	-52	16	Posterior Cingulate
0	3852	5.83	36	-50	47	Inferior Parietal Lobue
		4.34	33	-50	38	Parietal Lobe
		3.72	50	-41	52	Inferior Parietal Lobule
0.007	2284	5.81	28	14	-14	Inferior Frontal Gyrus
		4.05	21	8	-11	Lentiform Nucleus
		3.96	38	24	-21	undefined
0.001	3414	4.86	9	23	34	Cingulate
		3.77	3	6	57	Superior Frontal Gyrus
		3.7	-1	27	56	Superior Frotnal Gyrus
0.015	1901	4.85	-2	-67	58	Precuneus
		4.12	13	-71	44	Precuenus
G		3.34	7	-71	56	Superior Parietal Lobule
0	12146	4.64	34	-82	15	Middle Occipital Gyrus
		4.47	-5	-100	8	Cuneus
		4.08	-7	-94	-2	Cuneus
0.001	3488	4.55	-3	-23	4	Extra Nuclear
		3.98	6	-7	6	Thalamus
		3.87	-15	-18	-4	undefined
0.007	2262	4.42	-35	0	54	Middle Frontal Gyrus
		3.55	-22	12	59	Middle Frontal Gyrus
		3.46	-44	-3	55	Middle Frontal Gyrus
0.006	2378	4.39	26	18	-3	Claustrum
		4.23	37	28	2	Inferior Frontal Gyrus
		3.59	42	31	-5	Inferior Frontal Gyrus
0	5135	4.2	-22	4	-7	Extra Nuclear
		4.02	-24	-7	-1	Lentiform Nucleus
		3.75	-22	-31	0	Thalamus
0.046	1455	4.03	43	-3	45	Precentral Gyrus
		3.42	26	5	51	Sub-Gyral
		3.11	22	10	56	Superior Frontal Gyrus
0.005	2539	3.76	57	-56	23	Supramarginal Gyrus
		3.49	56	-53	15	Superior Temporal Gyrus
		3.4	48	-63	9	Middle Temporal Gyrus

Table 9 Whole Brain Activations

fMRI ROI Analysis

We examined activation in the *a priori* defined VWFA (Figure 12) where we performed a repeated measures (adults/children group x typical/reversed letters) analysis of covariance (ANCOVA) with stimulus correlated motion and number of artifacts as covariates. There was a significant interaction between group and letter type (F(1, 23) = 7.77, p = .010). This interaction was further explored by comparing typical and reversed letters in adults and children separately. Adults showed significantly greater activation for reversed letters than typical letters (t(12) = 2.59, p=.02). Children showed no activation difference between typical and reversed letters (t(13) = .96, p=.35). Because the children covered a wide age range, we examined whether these effects correlated with age among the children. Age did not correlate with activation to letters (r(13) = -.07, p=.81), reversed letters r(13) = -.33, p=.24), or the difference between reversed and typical letters (reversed – letters) (r(13) = -.41, p=.14).

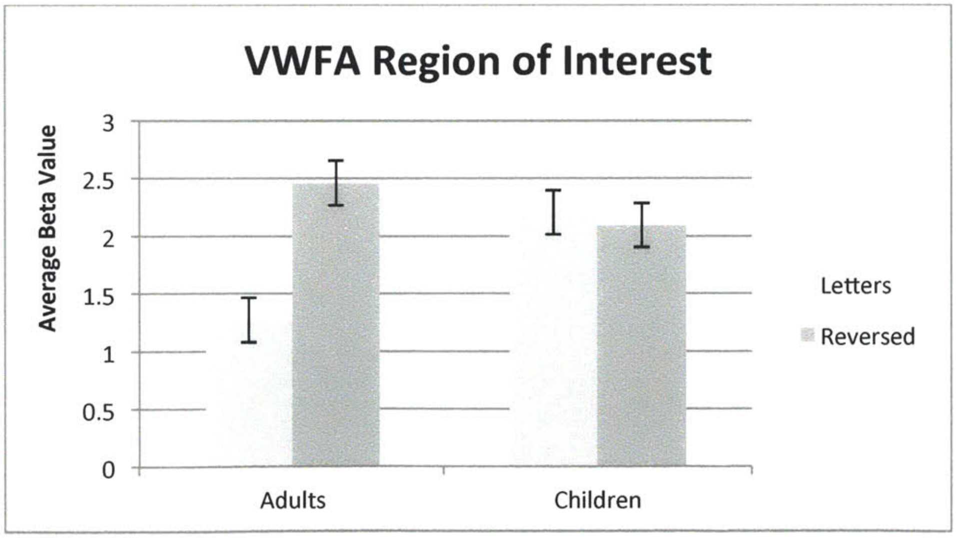


Figure 12 VWFA Region of Interest Analysis

Artifact Matched Analysis

A subgroup of children (N=7) and adults (N=7) were chosen who were matched for number of excluded time points (t(12) = .99, p=.34) in the letter reversal task. In this sample, children had a mean of 12.71 (SD = 6.02) excluded time points (5%) and adults had a mean of 9.29 (SD = 6.92) excluded time points (3%). Children had a mean average stimulus correlated motion of 0.09 (SD = .06) and adults had a mean stimulus correlated motion of 0.11 (SD = .01).

Results for the whole brain analysis were similar to those for the whole group, with fusiform activation for reversed > typical letters in adults, but not children, at a voxelwise threshold of p<.01 and FDR correction of p<.05. The adults > children comparison for the same contrast and threshold also resulted in left fusiform activation.

We performed the same VWFA ROI analysis on this subset of participants. There was a main effect of condition (F(1,11) = 5.82, p=.03) and a significant interaction between group and letter type (F(1,11) = 10.34, p = .008). In adults, activation to reversed letters trended to be higher than typical letters (t(6) = 1.93, p=.10), while children had no difference in activation (t(6) = .787, p=.46).

ERP Results

ERP results are illustrated in Figure 13. Both adults and children exhibited a P1 and N170 to both typical letters and reversed letters. For the P1 component, adults had a significantly more positive going wave for reversed letters compared to typical letters than did children (group x condition interaction: F(1,22) = 5.19, p = 0.03, ηp^2 = 0.19). This interaction reflects the fact that adults showed a significantly more positive going amplitude for reversed compared to typical letter (F(1,22) = 6.96, p = 0.02, ηp^2= 0.39), whereas children showed no reliable difference between these conditions on this component (all F's < 0.2, all p's > 0.6). The same pattern was also observed for the N170, however the difference between these conditions varied between the adults and children in the directionality (group x condition interaction ($F(1,22) = 5.15$, $p = 0.03$, $\eta p^2 = 0.19$). The N170 in adults is characterized by a more negative going wave for reversed letters than typical letters across the posterior electrodes (main effect of condition: $F(1,11) = 11.44$, $p = 0.006$, $\eta p^2 = 0.51$), whereas in the children the reversed and typical letter conditions did not differ significantly in amplitude ($F < 0.41$, $p > 0.5$).

Examining the timing of the N170 for typical and reversed letters, across both groups, the peak of the N170 occurred later in the children than the adults (main effect of group: $F(1,22) = 36.25$, $p < 0.001$, $\eta p^2 = 0.62$). In addition this group difference also interacted with whether or not the letters were reversed or normal (condition x group interaction: $F(1,22) = 6.31$, $p = 0.020$, $\eta p^2 = 0.22$). Examining each group individually revealed adults show significant differences in the peak latency of reversed compared to normal letters (main effect of condition: $F(1,11) = 16.01$, $p = 0.002$, $\eta p^2 = 0.6$), with reversed letters having a later peak latency than normally oriented letter. Children did not show a difference in latency between the two conditions (all F's < 1.1, all p's > 0.3).

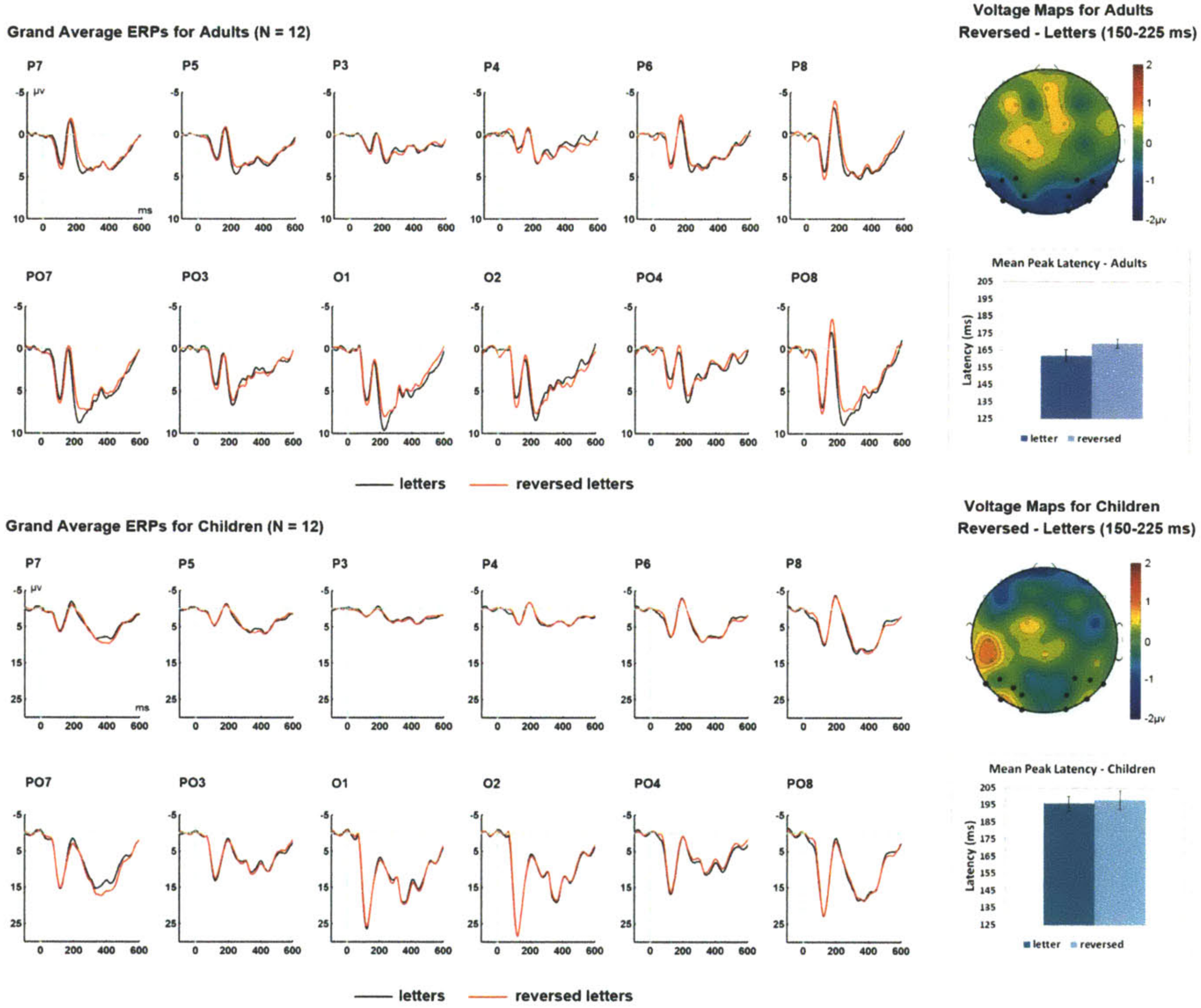


Figure 13 ERP Results

ERP and fMRI correlations

The mean amplitude difference on the N170 (computed by subtracting the amplitude of the response to typical letters from reversed letters) correlated significantly at electrode site P7 with the reversed letter - letter difference in the functionally defined VWFA (r(17) = -0.66, p = 0.004 (two tailed) (the correlation is negative because the N170 is a negative going effect) as well as with the mean amplitude at electrode site O1 (r(17) = -0.54, p = 0.03 (two-tailed)). Electrode site PO7 showed a marginally significant correlation with the VWFA activation (r(17) = -0.48, p = 0.05), whereas none of the other left hemisphere electrodes were significantly correlated. However, in each group separately there was not a correlation between ERP amplitude and VWFA activation, suggesting this correlation reflects the group difference observed on the N170.

Discussion

We found major developmental differences in fMRI and ERP brain responses to typical versus reversed letters in children ages 5-12 and young adults. Adults exhibited widespread fMRI activation for reversed relative to typical letters, including left fusiform regions associated with initial stages of reading, that was greater than that observed in children, who exhibited similar activation to typical and reversed letters. Adults also exhibited significant P1 and N170 ERP effects, greater for reversed than typical letters, while children exhibited no reliable differences between the two letter types for these ERP components associated with early stages of visual processing. The lack of any correlation between these findings and the ages of the children suggests that there is a remarkably long developmental progression for orientation-specific letter perception to become fully mature.

The children and adults were well characterized and equated on many measures, and therefore suitable for comparison. The two groups scored in the above average range on nonverbal IQ, reading, and reading-related, and therefore represent typical reading. The groups were similar on standardized (age-adjusted) nonverbal IQ. The adults performed significantly better on all reading and reading-related measures, thus exhibiting the expected benefits of an average of about 13 more years of reading experience and other maturation. The two groups were, however similar on age-standardized scores, with the children sometimes exhibiting a better score. Thus, it appears likely that brain differences reflect typical developmental differences.

Behavioral Findings

As often occurs, there were behavioral differences during scanning between children and adults. Children made more errors and had slower responses, and moved more in the scanner than did adults. The direct influence of performance on ERP and fMRI measures were limited in that the vast majority of trials (91% of localizer trials, 92% of letter reversal trials) involved stimuli for which no response was required. In regards to the contrast between typical and reversed letters, it seems unlikely that the worse performance of the children influenced findings because there was no interaction between age and condition (i.e., error rates and slowed responses were similarly worse for typical and reversed letters).

The developmental differences in brain responses also occurred in the context of specific tasks demands. Participants had to decide whether each stimulus was colored green or black, and respond only for the small minority of trials on which the letters were colored green. Thus, the orientation of each letter stimulus was independent of the required judgment, and there was no need to make explicit orientation judgments. Therefore, brain responses were unlikely to reflect higher-order cognitive processes or explicit analyses of letter orientation.

fMRI Findings

With fMRI, adults showed extensive activation for reversed letters compared to typical letters not only in the ventral visual “word form” stream, but also in the parietal lobe, and middle and superior frontal gyrus. The greater response for reversed letters may reflect an attentional difference between relatively novel reversed letters (that are almost never seen) and typical letters that are often seen and processed relatively fluently and automatically. In contrast, with the sole exception of a region in the right middle frontal gyrus, the children exhibited activations that were greater for typical than reversed letters (the opposite of adults). Greater activation in children for typical letters occurred not only in visual areas, but also in the left superior temporal gyrus and left inferior parietal lobule, two regions thought to be engaged in the phonological processing (Buchsbaum, Hickok, & Humphries, 2001; Hickok & Poeppel, 2007; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002). The greater activation for typical letters may reflect greater allocation of resources (i.e., less automaticity) for processing print in children as evidenced by studies reporting that children often have stronger activation than adults to words in the occipitotemporal reading network (Brown et al., 2005; Church, Coalson, Lugar, Petersen, & Schlaggar, 2008; Price & Devlin, 2011; Schlaggar et al., 2002).

Another possibility is that adults intentionally or incidentally rotated the reversed letters in an attempt to read them. This might be an alternative explanation for the activation of the inferior parietal lobule and superior frontal gyrus for reversed letters compared to typical letters in adults, as these regions have been reported to be active in neuroimaging studies of mental rotation(Alivisatos & Petrides, 1996; Cohen et al., 1996; Jordan, Heinze, Lutz, Kanowski, & Jäncke, 2001; Zacks, 2008).

Developmental fMRI studies comparing children and adults face a number of methodological issues. One issue is the combination of brains that differ anatomically with age into a common space for statistical analyses. For fMRI analysis, we normalized individual brings to an MNI adult template. In general, it has been shown that such normalization creates registration error that is lower than typical (including the present study) functional imaging resolution (Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). Further, the specific normalization method used in the present study (ANTs) has been shown to have registration error between children (age 4-11) and adults that is lower than our functional imaging resolution (Ghosh et al., 2010). This makes it unlikely that differences between children and adults might have resulted from lower quality normalization in the children.

A second important issue in developmental fMRI is the common finding that children have more artifactual time points rejected due to motion and other sources of artifact. Indeed, we found that children had a significantly greater number of rejected fMRI timepoints than did adults. For several reasons, however, we believe that these age-correlated differences in outlier data points did not spuriously produce our findings. First, we carefully eliminated outlier data points, and it has been shown that such elimination can minimize age-related confounds (Power, Barnes, Snyder, Schlaggar, & Petersen, 2011; Satterthwaite et al., 2012). Second, both a ROI and whole-brain analyses employing artifact-matched subsets of children and adults showed the same patterns of results as the overall sample. Third, the pattern of whole-brain results (greater activation for reversed letters in adults versus greater activation for typical letters in children) is an unlikely consequence of movement. Finally, ERP measures are not sensitive to the same sources of measurement difficulty (indeed, children exhibit larger ERP responses than adults) as fMRI measures, and the ERP measures also revealed large differences between children.

ERP Findings

Children and adults first diverged in the electrophysiological pattern they showed for letters and reversed letters in the P1 component. Adults had a larger amplitude P1 response for reversed than typical letters, whereas the children had no significant difference in response to reversed and typical letters. The P1 component is thought to reflect early, low-level featural processing that is not specific to stimulus content (Tarkiainen, Cornelissen, & Salmelin, 2002). However, some studies have found that the P1 can be modulated by meaning, with real objects engaging more attention than non-objects (e.g., Beaucousin et al., 2011). In addition, P1 differences have been observed when stimuli are presented in familiar versus unfamiliar visual formats (Rosazza et al., 2009). Therefore, this early difference between children and adults may be reflecting sensitivity in the adults to the orientation that drives more attention to the reversed letters compared to normally oriented letters, whereas in the children, this reversal is less salient.

Children and adults also exhibited significant differences in the N170 ERP component, with adults, but not children, showing a differential response to typical and reversed letters. The N170 response to words is associated with reading development. Studies have reported that pre-reading kindergartners showed no N170 differences between symbols and words in kindergarten, but by second grade typically reading children showed a left lateralized N170 difference between words and symbols; in contrast second-grade dyslexic children failed to show the N1 difference (Maurer et al., 2007; 2009). These findings support a relation between the N170 and the tuning of orthographic representations. The finding that there was a relation between the magnitudes of the N170 response and activation in the functionally defined VWFA in the same participants is consistent with intracranial electrophysiological evidence that the N170 response is generated in the fusiform cortex (Allison et al., 1999; Proverbio & Adorni, 2009).

There are few ERP studies investigating the effect of letter reversal, and those few have focused on mental rotation and later ERP components such as the N400 (Hamm et al., 2004; Núņez-Peņa & Aznar-Casanova, 2009). The typical finding in these studies is a posterior negativity for mirror-reversed or rotated letters compared to normally oriented letters. The present study examined more incidental or automatic perception of reversed letters rather than intentional rotation. The general pattern of ERP findings in adults, however, is similar to a finding that adults show different P1 and N170 responses to mirror-reversed and typical letters (Milivojevic, Hamm, & Corballis, 2011).

The finding that adults showed early ERP differences for reversed versus typical letters, and that the children did not show such differences, supports the view that the developmental brain differences observed in the fMRI study are unlikely to be explained by later-stage feed-back or rotation operations. Rather, the early ERP differences suggest that children have a less mature early-stage orthographic process in letter identification.

Conclusions

The present findings suggest that there is a remarkably long developmental process for the differential visual perception of typical and reversed letters. Children up to 12 years of age exhibited no P1 or N170 ERP differences for the two kinds of letters, whereas adults exhibited large and reliably greater responses for the reversed letters. FMRI revealed that the children exhibited no difference between the two kinds of letters in many brain regions, and sometimes exhibited greater activation for typical than reversed letters. In sharp contrast, the adults exhibited widespread activation for reversed relative to typical letters. These fMRI activation differences were observed in whole-brain analyses as well as ROI analyses focused on an independent functional localization of the putative VWFA, the first brain region differentially sensitive to words relative to many other visual stimuli.

These findings are surprising because they occurred for typically reading children (actually above-average reading children) after years of reading experience. These years of reading experience included countless exposures of typically oriented letters, and very few exposures to reversed letters. Yet, these children exhibited almost no difference in ERP or fMRI responses to typical versus reversed letters, whereas the adults exhibited much greater responses to the unusual reversed letters than the typical letters. The ERP findings indicate that these developmental differences are apparent within 100 msec of seeing the letters, and persist through the critical early stages of letter and word perception. The lack of an age correlation among the children indicates that a great deal of maturation must occur through adolescence. Of course, reading typically involves intentional perception of strings of letters in the context of text, rather than incidental perception of isolated letters. Nevertheless, the remarkable “brain blindness” to letter orientation is consistent with the view that letter perception begins developmentally with visual processes that are orientation insensitive. This late developmental timetable is not unknown in language development. It has been reported that adult-like categorical perception of native phonemes remains immature through at least age 12 (Hazan & Barrett, 2000).

Our findings on letter reversal can be interpreted in the light of the more general visual object recognition system. Reading is a relatively new evolutionary skill, likely relying on object recognition abilities. While the object recognition system is tuned to recognize objects regardless of mirror translations, this trait of the object recognition system is disadvantageous for reading. The observation that children often make reversal mistakes (not realizing letters have a correct orientation) provides ecological evidence that acquiring this skill utilizes, in some part, components of the object recognition system. Part of becoming a skilled reader requires involves understanding and establishing representations of letters that are orientation specific.

In the field of object recognition, several lines of evidence have shown that the human visual system generalizes between objects and their mirror images. The ability to recognize objects from various view-points has advantages in perceiving one’s environment, allowing one to identify a potential threat from many different views. In primates, single-cell recordings from the inferior temporal (IT) cortex show invariance to mirror images (Logothetis, Pauls, & Poggio, 1995). Brain imaging studies further support that the visual system generalizes across mirror reversals (Eger, Henson, Driver, & Dolan, 2004; Vuilleumier, Schwartz, Duhoux, Dolan, & Driver, 2005).

While mirror generalization is an adaptation for viewing naturalistic surroundings, it is a handicap when it comes to reading. In the majority of writing systems, orientation matters for letter identity. Therefore, learning to read requires selectively unlearning mirror generalization for letters, the most basic level orthographic representation involved in reading. The present study indicates that “unlearning” visual mechanisms that are orientation-insensitive and fruitful for object recognition in general requires a surprisingly long developmental period that extends at least in early adolescence.

Chapter 4: Left Occipitotemporal Selectivity for Words in Children and Adults

The visual word form area is well accepted to be an important part of the automatic reading pathway (Jobard et al., 2003). However, the exact nature of its selectivity remains under debate. While much research has focused purely on VWFA selectivity for different types of linguistic stimuli, other research has focused on whether the region is specialized for words compared to other non-linguistic categories of visual stimuli.

An important factor when studying selectivity is the contrast used to define the region, which can range from low level visual controls to complex visual stimuli. On one end of the spectrum, comparing words to checkerboards or rest yields robust activation in the left ventral visual stream (L. Cohen et al., 2002). Although this contrast controls for some minimal visual properties, words differ from checkerboards or fixations in many ways, including nameability, semantics, and visual coherence. Thus, the VWFA could be responding to any of those differences when preferentially activating to words relative to a low-level visual stimulus. On the other end of the spectrum, researchers have used objects, which, like words, are nameable, have meaning, and have a distinct visual shape.

A particularly important issue is whether the left occipitotemporal region described as the VWFA is specialized for words, and this specialization has been examined by contrasts between words and objects because words and objects are so similar in multiple dimensions. Findings in regard to preferential activation for words relative to objects have been notably mixed. One study using high-resolution fMRI imaging, found left fusiform activation for words relative to objects in over 85% of adults (Baker et al., 2007). Another study found that when stimuli were controlled for luminance, contour length, and number of features, word selective regions were found in not only the VWFA, but in also early visual regions (V1/V2, V3/V4) (Szwed et al., 2011). However, other researchers have argued against VWFA specialization for words relative to objects. One study found that activation for words relative to objects do not replicate within subjects between different scans, and are were interpreted as reflecting false positives (Wright et al., 2008). Other researchers argue against the idea of visual specialization for words, arguing instead that activation to words and pictures stem from top-down semantic influences. They note that the region is active in many non-reading tasks, including object naming, color naming, braille reading, and semantic processing of auditorily presented words (Price & Devlin, 2003). The idea of top-down semantic influence is also supported by the finding that cross-modal (picture/word) priming reduces activation in the left occipital temporal region by the same magnitude as word/word priming (Kherif et al., 2011).

There is some evidence that reading acquisition increases the selectivity of the VWFA. In a study of illiterate adults and adults of various reading levels, better readers were found to have more selective word form areas, with response to checkerboards and faces in the VWFA region decreasing with reading skill (Dehaene, Pegado, et al., 2010). Another study found a similar result in pre-reading children. Surprisingly, activation to letters in the left fusiform gyrus did not correlate with letter naming skill, but letter naming skill was negatively correlated with activation to a nonpreferred category (faces), suggesting that increased skill in face and letter recognition is associated not with enhancing activation to preferred stimuli, but with pruning back activation to unrelated stimuli. (Cantlon et al., 2011).

In our study, we explored the nature of VWFA selectivity in development. Using both a strict contrast of words compared to objects, as well as a looser contrast of words compared to scribbles, we compare selectivity in children and adults.

Methods

Participants

Participants were 20 children (10 male; Mean age 9.50, age range 7-12) and 20 adults (10 male; mean age 21.80; age range 19-30) with no history of reading difficulty were recruited from the university and surrounding community. Participants were required to have been exposed to English from birth, and not to have been exposed to any other language before the age of two. In addition, they were required to have scored above a 85 standard score on at least three of the following four tests: the Woodcock Reading Mastery Test (WRMT) Word ID, the WRMT Word Attack, Test of Word Reading Efficency (TOWRE) Sight Word Efficiency Subtest, and the TOWRE Phonetic Decoding Efficiency subtests. Participants also had to score above a standard score of 85 on the Kaufman Brief Intelligence Test (KBIT). Age and reading score measures are listed in Figure 14.

Behavioral and Reading Scores

Group	Mean	Std. Deviation

Age	Adults	21.80	2.86
	Children	9.5*	1.40
WRMT Word Attack Raw	Adults	39.50	3.03
	Children	35.4*	4.55
WRMT Word Attack SS	Adults	108.20	11.83
	Children	116.95*	12.15
WRMT Word ID Raw	Adults	100.10	2.47
	Children	81.45**	10.13
WRMT Word ID SS	Adults	107.65	6.26
	Children	116.7*	10.86
TOWRE Phonemic Detection Efficiency Raw	Adults	56.90	5.80
	Children	42.9**	8.66
TOWRE Phonemic Detection SS	Adults	105.80	10.25
	Children	115.6*	10.85
TOWRE Sight Word Extraction Raw	Adults	98.15	6.84
	Children	76.1**	10.41
TOWRE Sight Word Extraction SS	Adults	103.70	10.57
	Children	115.7*	11.83
KBIT Nonverbal Raw	Adults	43.40	1.14
	Children	36.85**	4.67
KBIT Nonverbal SS	Adults	122.00	5.71
	Children	122.55	12.87

*p<.05 ** p<.001

Figure 14 Age and Reading Scores

Informed consent for participation in the study, approved by the MIT Institutional Review Board was obtained from all participants. Adults were compensated for their participation and children received gift cards to a book store for participating.

Stimuli

Stimuli consisted of words, line drawings of faces, line drawings of objects, and scribbles (196 each). To control for contour structure and spatial frequency, stimuli were run through a computer program that reconstructed the images as dot patterns

Words were all nouns ranging from 3 to 8 letters long (avg = 4.6). Average HAL frequency according to the English lexicon project was 27670 (SD = 124497). Statistics for two words, 'yoyo', and 'bagel' were not available and thus were not included in the average. All stimuli were divided into two matched lists that were counterbalanced between participants. The words in one list were the names of the line drawings presented in the other list, and vice versa. Black and green versions of all stimuli were created for the task (described below). Stimuli were presented in a box that subtended roughly 4 degrees visual angle.

Procedure

In each trial, participants were presented with the stimulus for 200 ms, followed by 800ms of a blank screen. Stimuli were presented in black or green in a block design fashion, each consisting of 14 trials (blocks of 14 s). Participants were instructed to press the response button anytime a stimulus was green, which occurred one or two times per block. Between each block, a cartoon alien flashed on screen for 2 seconds. Because this paradigm was also run on children, participants were told that the experiments were an attempt to teach the alien about color.

Participants were scanned in this experiment for two runs of four minutes and 26 seconds each. In the two runs combined, there were seven blocks of each condition, plus 6 fixation blocks.

FMRI Acquisition Parameters

FMRI scanning took place at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research at MIT. Imaging was performed using a Siemens 3T MAGNETOM Trio, A Tim System, (Siemens Medical Solutions, Erlangen, Germany) and a commercial Simens 32 channel head coil. High-resolution structural whole-brain images were acquired using a T1-weighted anatomical scan with motion correction (176 slices per slab; 1 mm isotropic voxel size; TR=2530ms; TE=1.64ms) (Tisdall et al., 2011).

Functional data were collected using a gradient echo T2*-weighted EPI sequence sensitive to the BOLD contrast (2mm isotropic voxel size; TR = 2; TE = 30ms; slices). Slices were placed at an oblique orientation parallel to the AC-PC line. We made sure that the lowest part of the occipital lobe and the bottom part of the temporal lobe in the left hemisphere (including the temporal pole) were covered. The uppermost part of the cortex in the frontal and parietal lobes were covered as well. All in all, slices covered the entire cortex (with the exception of the dorsal portion of the motor cortex in some participants) and usually parts of the cerebellum.

FMRI Analysis

The analysis was performed with SPM8, FreeSurfer, Artifact Rejection Toolbox (ART) and Advanced Normalization Tools (ANTS) using Nipype and bash scripts for workflow design and execution. Functional images were realigned to the mean image and smoothed with a 4mm

FWHM Gaussian kernel. The functional image co-registration to the 3D anatomical was performed in Freesurfer using a surface based registration algorithm (ref). Structural and functional images were normalized to the Montreal Neurological Institute (MNI) space using ANTS (Klein et al., 2009). Data was high pass filtered with 128/s cutoff. In the first level analysis, each condition was convolved with a canonical HRF. A one-lag autoregression (AR(1)) model was used to correct for serial (i.e., temporal) autocorrelations. The ART toolbox was used to detect motion outliers. Timepoints whose position deviated from the previous by more than 1 mm, or whose average signal intensity deviated from the series average by more than 3 standard deviations were added to the model as nuisance regressors.

Random-effects analyses were performed by entering the SPM contrast images aligned to the subject specific ANTS normalized brain from the first level analysis into a second-level analysis of covariance, with stimulus correlated motion and number of artifacts as covariates. The ANTs normalization resampled the functional images to a voxel size of $1mm^3$. Analysis was restricted to the left occipitotemporal region. The threshold for activation was set at a voxel-wise uncorrected level of $p<.05$, with an FDR cluster correction of $p<.05$.

Results

In-scanner Behavioral Measures

Overall accuracy (measure includes correct rejections), percentage of probes detected, and reaction time for children and adults are listed in Table 10. Mixed model ANOVAs with 4 conditions as a within-subject factor and 2 age groups as a between subject factor were run for each measure.

Adults (99.4%) tended to be more accurate overall than children (99.1%) [F(1,38) = 3.28, p=.078)]. The assumption of sphericity was violated for condition (chi-square = 15.13, p = .010), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .810). There was no main effect of condition [F(2.43,92.37) = .36, p=.74], and no condition by group interaction (F(2.43, 92.37) = .21, p=.86).

% Accuracy	Words	Faces	Objects	Scribbles	Overall
Adults	99.44 (1.07)	99.54 (0.70)	99.39 (0.90)	99.34 (0.89)	99.43 (0.63)
Children	98.93 (1.22)	99.18 (1.13)	98.98 (1.05)	99.13 (1.00)	99.06 (0.66)

Table 10 Overall Accuracy

Adults (95%) did not differ from children (93%) in the percentage of probes detected [F(1,38) = 1.03, p=.32]. The assumption of sphericity was violated for condition (chi-square = 17.89, p = .003), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .79). There was no main effect of condition [F(2.36, 89.65) = 1.18, p=.32], and no condition by group interaction (F(2.36,89.65) = .49, p=.64).

% Probes Detected	Words	Faces	Objects	Scribbles	Overall
Adults	96.11 (10.37)	96.67 (5.22)	93.33 (9.12)	92.78 (9.72)	94.72 (6.04)
Children	91.11 (13.77)	95 (9.86)	92.78 (9.72)	91.67 (11.33)	92.5 (6.99)

Table 11 Percentage Probes Detected

Adults (536 ms) were on average reliably faster than children (665 ms) [F(1,38) = 44.62, p<.001]. For reaction time, the assumption of sphericity was violated for condition (chi-square = 17.67 , p = .003), and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (epsilon = .74). There was a main effect of condition [F(2.22, 84.22) = 3.73, p=.024], and no interaction between group and condition [F(2.22,84.22) = .50, p=.63]. Paired t tests revealed that response to word probes (620ms) was significantly slower than response to face probes (590ms) [t(39) = 2.69, p= .011] and scribble probes (595ms) [t(39) = 2.37, p=.02]. No other pairwise comparisons were significantly different.

Reaction Time (ms)	Words	Faces	Objects	Scribbles	Overall
Adults	550 (64.42)	530 (51.50)	534 (54.2)	533 (64.8)	536 (54)
Children	691 (115)	650 (63)	669 (70)	658 (75)	665 (64)

Table 12 Reaction Time

Stimulus Correlated Motion and Number of Artifacts

Children averaged 18.80 (SD =16.75) rejected timepoints as defined in the methods section across both runs of the task, while adults averaged 3.60 (SD= 3.20) rejected timepoints. Levene's test indicated that the two groups had unequal variances for number of rejected timepoints (F(38) = 27.85, p<.000). An independent samples t test (equal variances not assumed) found that children had significantly more rejected timepoints (t(20.387) = 3.99; p =.001). Children (M =.10; SD = .024) and adults (M = .11; SD = .023) did not differ significantly (t(38) = 1.15, p=.26) in the amount of stimulus correlated motion. Outliers and stimulus correlated motion were added as covariates in the between groups whole brain and ROI analyses.

Activation in Left Occipitotemporal Region

For the words > scribbles contrast, both adults and children showed significant activation in the left occipito-temporal region, and there were no between group differences in the left occipitotemporal region (Figure 15). For the words > objects contrast, adults showed significant left occipital-temporal activation. Children did not exhibit any above-threshold activation. Comparison of adults and children revealed greater left occipitotemporal activation for adults, as well as greater activation for adults along the left temporal lobe. There was no above threshold activation in the occipital or temporal lobes for the children>adults contrast (Figure 15).

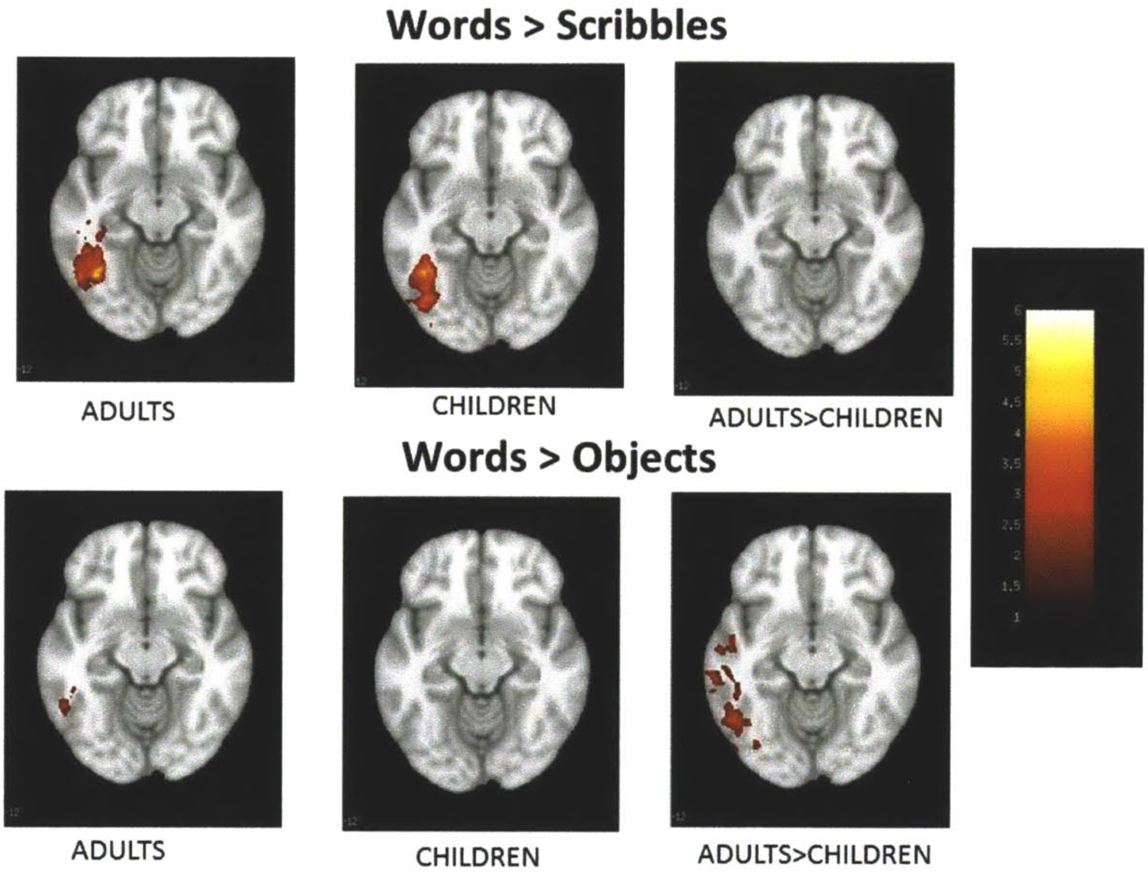


Figure 15 Occipitotemporal Activation to Words Compared to Scribbles and Objects

We further explored activation for specific conditions by extracting activation levels from the group-defined clusters. In the cluster defined by the words > scribbles contrast in adults, adults and children showed similar patterns, with positive activation for words and much lower activation to scribbles (Figure 16). Similar patterns were obtained when values were extracted from the cluster defined by the words>scribbles contrast in children (Figure 16).

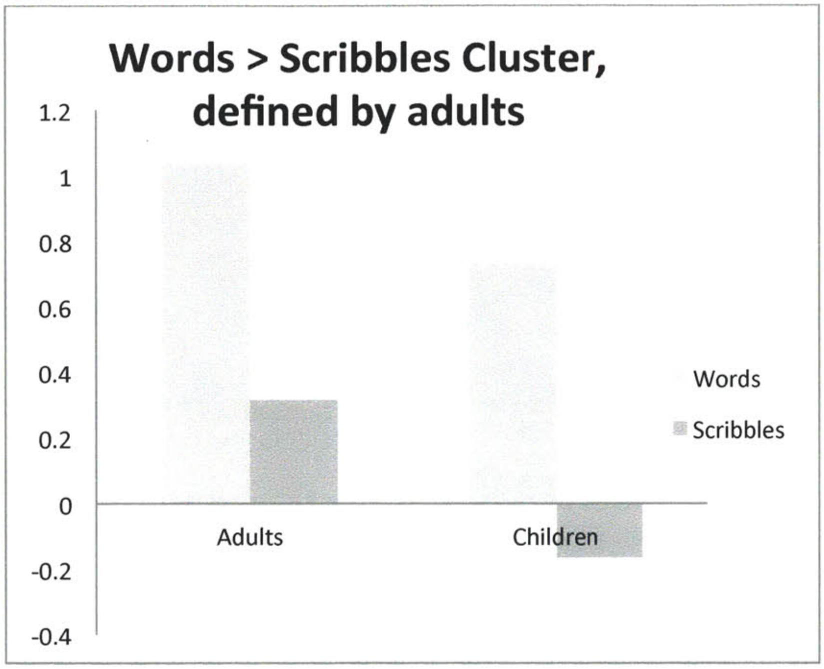


Figure 16 Activation in Words > Scribbles Cluster, defined by adults.

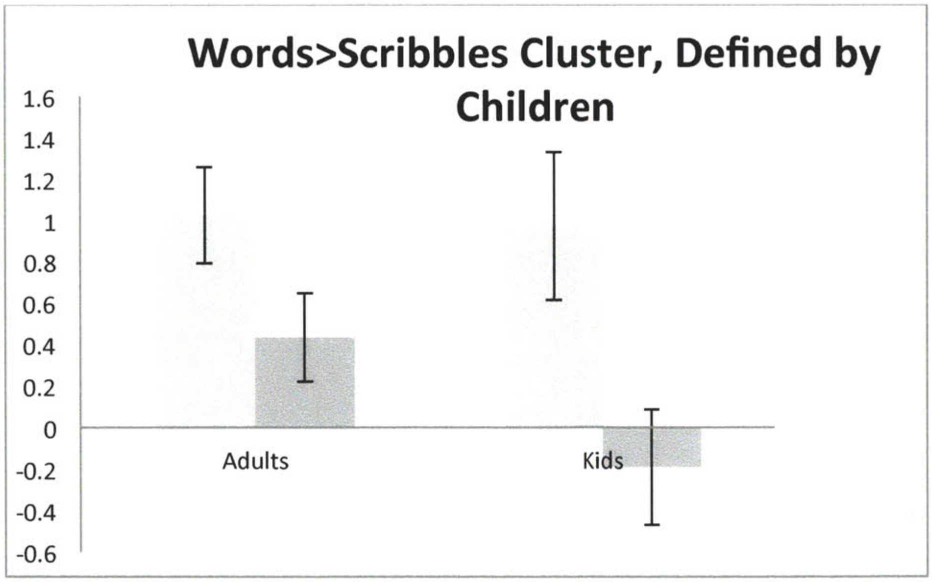


Figure 17 Words > Scribbles Cluster, Defined by Children

We also extracted activation values in both children and adults from the cluster defined by the words > objects contrast in adults. In this case, adults showed positive activation for words and much lower activation to objects. Children, on the other hand, showed activation close to baseline to both words and objects (Figure 18).

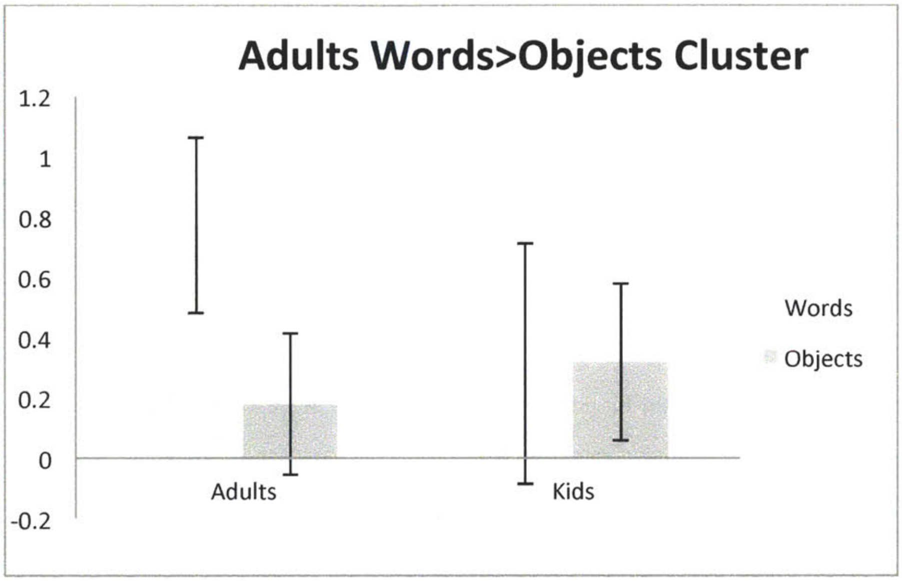


Figure 18 Activation in the Words>Objects cluster, defined by adults.

Finally, we looked at activation in the cluster defined by the direct comparison between adults and children for the words > objects contrast. In this cluster, adults show positive activation for both words and objects. Children, on the other hand, showed positive activation for objects and near-baseline activation to words. This suggests that children are deactivating to words in the temporal portions of this cluster.

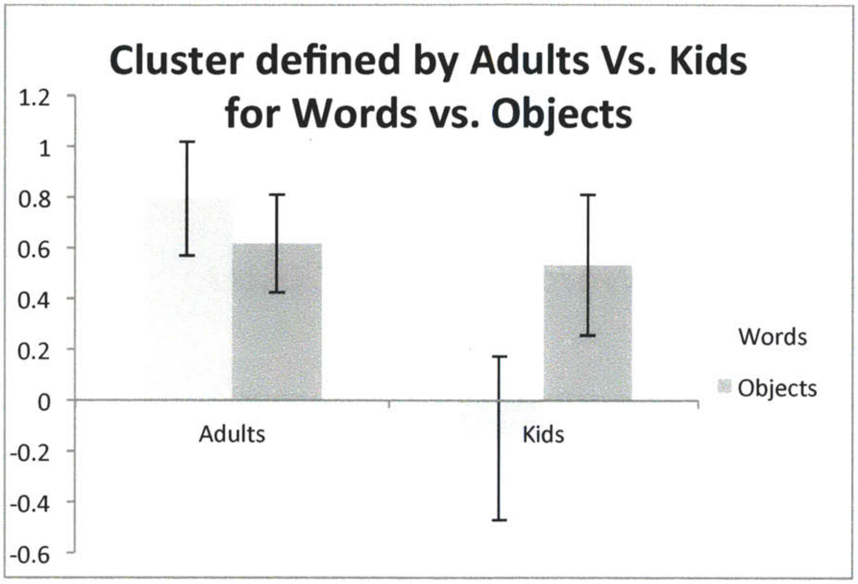


Figure 19 Activation in the cluster defined by the the adult > children comparison of the words > objects contrast.

Artifact Matched Analysis

A subgroup of children (N = 12) and adults (N=12) were chosen who were matched for number of excluded time points (t(22) = 1.28, p =.21). In this sample, children had a mean of 7.50 (SD = 4.87) excluded time points (3%) and adults had a mean of 5.41 (SD = 2.87) excluded time points (2%). Children had a mean average stimulus correlated motion of 0.11 (SD = .02) and adults had a mean stimulus correlated motion of 0.11 (SD = .02). Adults and children did not differ in stimulus correlated motion (t(22) = -.01, p=.92).

In the whole brain analysis for the subgroup, both adults and children showed words > than scribbles activation in the left occipitotemporal region, and there was no difference between the groups when adults and children were compared directly. For the words > objects contrast, neither adults or children showed occipitotemporal activation. However, when the adults and children were compared directly, there was activation in the occipital temporal region as well as the temporal lobe.

Discussion

In this study, we compared selectivity in the left occipital temporal region between children and adults. We found that for a less selective contrast, words > scribbles, children displayed adult-like activation patterns. However, when words were compared with objects, adults and children displayed different patterns, with adults showing greater word specialization than children.

While specialized visual regions for processing categories of visual stimuli such as faces (Kanwisher et al., 1997), places (Epstein & Kanwisher, 1998), and body parts (Downing et al., 2001) have been discovered, the visual word form area is unique in that words are a recent cultural invention going back only a few thousand years. Thus, it is assumed that the visual word form area could not have formed via evolutionary processes. Some researchers have therefore suggested that visual word processing takes advantage of existing portions of the object recognition system, perhaps recycling existing visual regions predisposed to visual stimuli that share visual properties with words (Dehaene & Cohen, 2007). Possible properties include high spatial frequency (Bilenko, Rajimehr, Young, & Tootell, 2008), central (as opposed to peripheral) location in the visual field (Hasson et al., 2002) a preference for line junctions to line midsegments(Szwed et al., 2011), and/or a hemispheric proximity to language (Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2007; Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010). There is also some evidence that writing systems have evolved to fit certain visual parameters. Writing systems across cultures have some similarities – they all average about three strokes per character, and the topological configurations of characters reflect that of natural images(Changizi & Shimojo, 2005; Changizi, Zhang, Ye, & Shimojo, 2006).

These results are consistent with a view of gradual specialization in the occipito-temporal region. The school-age children we tested displayed adult-like activation when comparing words to a considerably different low-level visual control. We do not know if this is because the occipital-temporal region is already well tuned enough to the low-level features of words so that reading experience is not required to engage the region over scribbles, or because the few years of experience that our children had already received was sufficient. However, with the more selective control, children did not display the specialization seen in adults, suggesting that more years of reading experience are required to develop specialization of words compared to objects.

Developmental fMRI studies comparing children and adults face a number of methodological issues. One issue is the combination of brains that differ anatomically with age into a common space for statistical analyses. For fMRI analysis, we normalized individual brings to an MNI adult template. In general, it has been shown that such normalization creates registration error that is lower than typical (including the present study) functional imaging resolution (Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). Further, the specific normalization method used in the present study (ANTs) has been shown to have registration error between children (age 4-11) and adults that is lower than our functional imaging resolution (Ghosh et al., 2010). This makes it unlikely that differences between children and adults might have resulted from lower quality normalization in the children.

A second important issue in developmental fMRI is the common finding that children have more artifactual time points rejected due to motion and other sources of artifact. In our main sample, children had a greater number of rejected fMRI timepoints (due to motion/signal outliers) than adults. There is evidence that such measurement problems can yield spurious developmental findings in fMRI studies, but careful elimination of such data can minimize this problem (Power et al., 2011; Satterthwaite et al., 2012). When we conducted our analysis with outlier matched subsets, the only difference in results was that adults no longer showed any words >object activation in the left occipitotemporal region. We believe this is due to lower power, though further studies will be needed to be confirmed this. Importantly, however, our results for children in the left occipitotemporal region did not differ for our artifact-matched subsets, nor did the between group comparison.

Chapter 5: Conclusion

We have reported three studies on the visual word form area. The first study found that selectivity patterns in the VWFA were highly dependent on top-down influences. Using an implicit attentional manipulation, we found that VWFA activation to words, pseudowords, and consonant strings did not differ in the attended condition. In the unattended condition, however, the VWFA responded more to words than pseudowords or consonant strings.

The latter two studies found evidence of a prolonged developmental course in the visual word form area. In one study, we found that adults had greater activation to reversed letters than typical letters in both the VWFA region of interest and in EEG P1 and N170 amplitudes. Children, on the other hand, showed no difference in response to letters vs. typical letters in any of those measures.

In our last study, we compared sensitivity (word activation vs. squiggles) and selectivity (for words compared to objects) in the VWFA. Adults and children had comparable regions of activation for words compared to scribbles – thus, we found that adults and children had similar sensitivity. In the case of selectivity, however, adults had a brain region selective for words vs. objects, while children did not.

These results suggest that VWFA development continues past the maximum age of our sample (12 years), but there remain plenty of unanswered questions about the formation of the visual word form area. VWFA development can be thought of as two related processes. First, even before reading acquisition, characteristics of the underlying object recognition cortex predispose the left occipitotemporal to becoming specialized for words. Thus, the VWFA develops in a similar location across individuals and languages (Bolger et al., 2005; Tan et al., 2005). But with prolonged reading experience, the region develops further selectivity for words. This shows through in our developmental studies as improved discrimination between typical and reversed letters in the left occipitaltemporal region in adults, as well as the development of a word > objects region in adults.

Studies have already provided hints on low level characteristics that may predispose a region for word processing. For example, Hasson and colleagues have shown that the VWFA overlaps with visual regions specialized for processing stimuli shown at fixation (Hasson et al., 2002). Szwed et al (2011) found that that word-specialized regions overlapped with regions that preferred processing line junctions (as opposed to midsegments). Studies also suggest a preference for high spatial frequency in the visual word form area (Bilenko et al., 2008; Woodhead, Wise, Sereno, & Leech, 2011).

Developmental studies probing the contribution of these low-level features would provide further insight. One could easily manipulate parameters such as spatial frequency or contour structure in a VWFA localizer and investigate how those changes affect activation in prereading children. Likewise, one can investigate how activation patterns change as reading skill increases.

In our study on attentional effects, we found that the visual word form area is highly susceptible to top-down influences. This has implications for the two developmental studies we have reported. In designing the developmental experiment, we made an effort to control for top-down influences as much as possible. To that end, the task was designed to be easy, and the stimulus presentation was very short (200ms) in order to minimize strategic differences between adults and children. However, because it is impossible to ensure complete elimination of strategic differences, our developmental results would benefit from convergent evidence using different paradigms. It is likely that an alternative task for our developmental studies may have resulted in different activation patterns. For example, in our letter reversal experiment, we found that adults had greater activation to reversed letters compared to typical letters. However, had the stimuli in our experiment been masked, activation to unfamiliar reversed letters may have been lower than typical letters because the participants would no longer register conscious surprise.

The VWFA's susceptibility to attentional influences raises the question of whether stimulus-based approaches are worth pursuing. While bottom-up selectivity of the VWFA remains a worthwhile question, our results suggest that it would be prudent to control for top-down effects as much as possible. Furthermore, in addition to focusing solely on stimulus characteristics, it may be worthwhile to focus instead on the VWFA's role in relation to the rest of the reading network. Functional connectivity analyses, for example, could be used investigate how stimulus category affects VWFA connectivity with the rest of the reading pathway (Reinke et al., 2008). Finally, convergent evidence using complementary techniques such as EEG and MEG will continue be helpful in sorting out the contribution of early and later processes.

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