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Age, Sex, and Verbal Abilities Affect Location of Linguistic Connectivity in Ventral Visual Pathway

Douglas D. Burman^{1,2}, Taylor Minas², Donald J. Bolger^{2,3}, and James R. Booth²

Douglas D. Burman: DBurman2@northshore.org; Donald J. Bolger: bolger.dj@gmail.com; James R. Booth: j-booth@northwestern.edu

¹Center for Advanced Imaging, NorthShore University HealthSystem, Evanston, IL 60201, USA

²Dept. of Communication Sciences and Disorders, Northwestern University, Evanston, IL 60208, USA

³Dept. of Human Development, Maryland University, College Park, Maryland 20742, USA

Abstract

Previous studies have shown that the *strength* of connectivity between regions can vary depending upon the cognitive demands of a task. In this study, the *location* of task-dependent connectivity from the primary visual cortex (V1) was examined in 43 children (ages 9–15) performing visual tasks; connectivity maxima were identified for a visual task requiring a linguistic (orthographic) judgment. Age, sex, and verbal IQ interacted to affect maxima location. Increases in age and verbal IQ produced similar shifts in maxima location; in girls, connectivity maxima shifted primarily laterally within the left temporal lobe, whereas the shift was primarily posterior within occipital cortex among boys. A composite map across all subjects shows an expansion in the area of connectivity with age. Results show that the *location* of visual/linguistic connectivity varies systematically during development, suggesting that both sex differences and developmental changes in V1 connectivity are related to linguistic function.

Keywords

fMRI; connectivity; development; language; IQ; sex; reading

1. Introduction

Reading requires the conversion of visual information about component shapes into a recognizable lexical form. Reading words engages the ventral stream of visual processing, particularly left hemisphere regions involved in the processing of orthographic information (Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Brem et al., 2006); see also reviews by (Donald J. Bolger, Perfetti, & Schneider, 2005; Cohen & Dehaene, 2004; Dehaene et al., 2010; Jobard, Crivello, & Tzourio-Mazoyer, 2003), as well as superior temporal and inferior parietal regions involved in phonological processing (Booth et al., 2002; Booth, Burman, Meyer, Lei et al., 2003; Booth, Mehdiratta, Burman, & Bitan, 2008;

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Corresponding author: Douglas D. Burman, Center for Advanced Imaging, Walgreen Building Suite G507, NorthShore University HealthSystem, Evanston, IL 60201, USA, DBurman2@northshore.org. Phone: 847-570-4578 Fax: 847-733-5990.

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Jobard et al., 2003; Turkeltaub & Coslett, 2010). Young beginning readers recognize words based upon holistic characteristics such as word shape, whereas older more advanced readers use a combination of whole-word recognition and detailed awareness of letter combinations and their phonological representations (Ehri, 1995; Ehri, 2005; Ehri & McCormick, 1998). These different strategies for word recognition areas are likely subserved by differential regions of cortex, regions which are highly interactive during word recognition and whose functional activity is highly correlated with task performance in various brain areas (Booth et al., 2008; Horwitz, Rumsey, & Donohue, 1998). Moreover, this interactivity develops as a function of experience and skill in young readers (Landi, Perfetti, Bolger, Dunlap, & Foorman, 2006), as orthographic and phonological processing in cortex is tuned to reflect the changing knowledge of spelling-to-sound relationships (D. J. Bolger, Hornickel, Cone, Burman, & Booth, 2008; Cao et al., 2010; Cone, Burman, Bitan, Bolger, & Booth, 2008; Maurer et al., 2006; Spironelli & Angrilli, 2009). These developmental changes in reading and language abilities should thus be reflected in changes in task-specific connectivity.

Interaction between visual and lexical areas is critical for reading. Visual processing in the ventral occipitotemporal region develops specificity for lexical stimuli during the acquisition of reading (Maurer et al., 2006), but this lexical specificity is delayed or absent in dyslexic children (Maurer et al., 2007; Maurer et al.) and pre-readers with low letter knowledge (Maurer, Brem, Bucher, & Brandeis, 2005). With difficulty converting visual information into phonology, dyslexic subjects show reduced responsivity to words (Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Salmelin, Kiesilä, Uutela, & Salonen, 1996), likely due to reduced connectivity between occipitotemporal visual regions and phonological areas (Horwitz et al., 1998; Ligges, Ungureanu, Ligges, Blanz, & Witte, 2010; Pugh et al., 2000; Quaglino et al., 2008; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000; van der Mark et al., 2011). Top-down lexical connections also modify occipitotemporal responses (Briem et al., 2009; Dikker, Rabagliati, & Pylkkänen, 2009; Foxe & Simpson, 2002; J. Liu et al., 2011; Pernet, Celsis, & Démonet, 2005; Quaglino et al., 2008; Yoncheva, Zevin, Maurer, & McCandliss, 2010), and may be essential to the acquisition of lexical selectivity within the ventral visual pathway (Dehaene et al., 2010). Connectivity from V1 reflects visual processing; changes in V1 connectivity during lexical tasks indicates where visual processing is first modified by lexical processes (a visual / lexical interaction).

Such psychophysiological interactions (Das et al., 2005; Friston et al., 1997) should reflect perceptual changes as readers mature and use different visual cues for word identification. Developmental differences in the size of lexical units used for word identification may be reflected in the *location* of task-specific connectivity due to the organization of visually-responsive cortex. Within the ventral stream of visual processing, visual information about component shapes is conveyed from the primary visual cortex (V1) to anterior regions in a hierarchical fashion, progressively sensitive to larger orthographic units (Cohen & Dehaene, 2004; McCandliss, Cohen, & Dehaene, 2003). For example, specificity for letters, syllables and words is seen within this ventral stream, extending from extrastriate occipital regions into the fusiform gyrus and inferotemporal cortex (Cohen et al., 2002; Kronbichler et al., 2007; Kronbichler et al., 2004; Pegado, Nakamura, Cohen, & Dehaene, 2010; Schurz et al., 2010), with selectivity for larger units appearing further anterior within this region (Cohen, Henry et al., 2004; Cohen et al., 2002; Dehaene et al., 2004; Tagamets, Novick, Chalmers, & Friedman, 2000; Tarkiainen, Cornelissen, & Salmelin, 2003; Vinckier et al., 2007). As children grow older and improve reading performance, linguistic connectivity may thus shift (or expand) from the temporal lobe into occipital cortex, reflecting an increased awareness of individual letter combinations. Alternatively, lateral temporal regions show stimulus specificity for smaller (or more centralized) objects than medial temporal regions (Hasson,

Harel, Levy, & Malach, 2003; Lerner et al., 2003; Levy, Hasson, Avidan, Hendler, & Malach, 2001); see also (Chao, Martin, & Haxby, 1999; Maguire, Frith, & Cipolotti, 2001); thus, increased awareness of letter combinations as children become better readers with age might instead result in a lateral shift (or expansion) of lexical connectivity within the temporal lobe. Such a shift would be analogous (but opposite in direction) to the lateral-to-medial shift in fusiform face processing with age with improvements in recognizing global features (Chao et al., 1999).

To demonstrate lexical changes in V1 connectivity, individual variability in language abilities must be considered. Several measures are potentially relevant. For example, the word ID and word attack subtests of the WJ-III are standardized measures of the ability to read words and pseudowords, respectively; if differences in connectivity account directly for differences in reading ability at a given age (e.g., via bottom-up processes), shifts in connectivity should be correlated with either or both of these scores. On the other hand, posterior or lateral shifts in connectivity may instead reflect top-down processes that reflect more general verbal abilities and experiences relevant to reading skills. For example, vocabulary influences reading comprehension and exception word reading (Ricketts, Nation, & Bishop, 2007). The acquisition of new vocabulary is itself influenced by orthographic knowledge (Ehri & Rosenthal, 2007), suggesting that visual areas involved in processing orthography interact with language areas involved in vocabulary acquisition. Vocabulary and knowledge of word similarities are both incorporated into verbal IQ (an age-normalized measure of verbal language abilities), and verbal IQ is correlated with both structural (Ramsden et al., 2011) and functional variability in cortical language processing (Everts et al., 2009; Lidzba, Schwilling, Grodd, Krägeloh-Mann, & Wilke, 2011). Because it reflects verbal abilities and knowledge relevant to reading, higher verbal IQ could result in either the posterior or lateral shift in connectivity (as described above).

The sex of a subject is also likely to be relevant. Developmentally, girls are generally more advanced for language (Bornstein, Hahn, & Haynes, 2004; Han & Hoover, 1994; Lynn, 1992; Mann, Sasanuma, Sakuma, & Masaki, 1990; Martin & Hoover, 1987; Martins et al., 2005; Undheim & Nordvik, 1992). During orthographic and phonological tasks, girls and boys differ in the lateralization of evoked potentials (Spironelli, Penolazzi, & Angrilli, 2010); furthermore, girls' fMRI activation within the left fusiform gyrus is greater than boys and correlated with performance accuracy, even after accounting for age and language skill (Burman, Bitan, & Booth, 2008). Thus, one may hypothesize that the primary focus of connectivity in the visual ventral stream depends on age, verbal IQ, and the sex of a subject.

Considering these influences, we wondered whether there are individual differences in language-specific connectivity within the visual system that could be relevant to reading. More specifically, is the location of maximal language-specific connectivity from V1 affected by age, sex or verbal IQ? To identify the earliest visual area involved in language function, this study examines regions in the ventral stream of children whose connectivity with primary visual cortex (V1) increases when making orthographic comparisons between words. The left occipitotemporal response to words depends on language lateralization (Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Rossion, Joyce, Cottrell, & Tarr, 2003; Spironelli & Angrilli, 2007), with laterality of language function in occipitotemporal regions increasing with age (Everts et al., 2009; Spironelli & Angrilli, 2009); thus, developmental changes in connectivity associated with language function should occur preferentially in the left hemisphere. In the current study, psychophysiological interactions are used to identify the region whose connectivity with V1 is most strongly modulated by the linguistic component of an orthographic comparison task (i.e., the connectivity maximum); the effects of age, sex, verbal IQ, and standardized reading scores on the location of this maximum

within the ventral stream of visual processing is then examined separately for the left and right hemispheres.

2. Methods

2.1. Subjects

Forty-two healthy children participated in the study (ages 9–15, mean 11.3, twenty females). Children were recruited from the Chicago metropolitan area; the Institutional Review Board at Northwestern University and Evanston Northwestern Healthcare Research Institute approved the informed consent procedures. Parents of children were given an interview to exclude participants having a previously reported history of intelligence, reading, attention, or oral-language deficits. All children were described as free of neurological diseases or psychiatric disorders and were not taking medication affecting the central nervous system. Children were native English speakers, with normal hearing and normal or corrected-to-normal vision. Included children were all right handed (mean = 78.2, range 50–90) according to the 9-item Likert scale questionnaire (–90 to 90, positive scores indicate right hand dominance).

Subjects fell into one of 4 age groups at the time of their testing (birthdays within 4 months of their specified age): age 9, 11, 13 or 15. Standardized intelligence test scores (Wechsler, 1999) showed an average full scale IQ of 116 (range of 94 – 146, SD = 12.6); Verbal IQ of 116.3 (range of 79–142, SD = 14.1); and performance IQ = 108.9 (range of 79–139, SD = 14.7). The verbal IQ component of this test includes subtests of Vocabulary and Similarities (verbal reasoning and concept formation). The average standardized reading score (Woodcock, Mather, McGrew, & Schrank) was 107.2 for nonword reading accuracy (range of 88–125, SD = 9.8) and 112 for word reading accuracy (range 95–130, SD = 9.6); the average mean standardized spelling score (Wilkinson, 1993) was 114.4 (range 90–140, SD = 11.4).

2.2. Experimental Task

The orthographic comparison task used in this study (elsewhere referred to as a “visual spelling task”) has been described in detail (Bitan et al., 2005; Booth et al., 2002; Booth, Burman, Meyer, Gitelman et al., 2003; Booth et al., 2004). Briefly, two words were presented visually in a sequential order. Each word was presented for 800 ms separated by a 200 ms blank interval; the position of the second word was jittered to avoid responses based solely on same/different visual features. A red fixation-cross appeared on the screen after the second word, indicating the need to make a response by pressing one of two buttons during the subsequent 2,600 ms interval. Participants determined if the rime (letter sequence from first vowel onward) was spelled the same in the two words. Participants used their right index finger to press a button for a ‘yes’ response and their right middle finger for a ‘no’ response.

This orthographic comparison task was presented in two runs, each presenting twenty-four unique word pairs that independently manipulated the orthographic and phonological similarity between words. The four resulting lexical conditions occurred with equal probability.

Two perceptual control conditions were used in which two symbol strings were presented visually in sequential order and the participant had to determine whether the strings matched. In the ‘Simple’ condition, the symbol string consisted of a single symbol, while in the ‘Complex’ condition the symbol string consisted of three different symbols. Timing and response parameters were the same as for the lexical conditions. Twenty-four items were presented in each perceptual condition, with half of them matching. In addition to the

perceptual control conditions, 72 fixation trials were included as a baseline. In the fixation condition, a black fixation-cross was presented for the same duration as the stimuli in the lexical and perceptual conditions and participants were instructed to press a button when the black fixation-cross turned red. The order of lexical, perceptual and fixation trials were optimized for event-related design (Burock, Buckner, Woldorff, Rosen, & Dale, 1998) and fixed for all subjects.

2.3. MRI Data Acquisition

Images were acquired using a 1.5 Tesla General Electric (GE) scanner, using a standard head coil. Head movement was minimized using vacuum pillow (Bionix, Toledo, OH). The stimuli were projected onto a screen, and viewed through a mirror attached to the inside of the head coil. Participants' responses were recorded using an optical response box (Current Designs, Philadelphia, PA). The blood-oxygen level dependent functional images were acquired using the echo planar imaging (EPI) method. The following parameters were used for functional images: time of echo (TE) = 35 ms, flip angle = 90 deg, matrix size = 64×64 , field of view = 24 cm, slice thickness = 5 mm, number of slices = 24; time of repetition (TR) = 2000 ms, 240 repetitions. A structural T1 weighted 3D image was also acquired (TR = 21 ms, TE = 8 ms, flip angle = 20° , matrix size = 256×256 , field of view = 22 cm, slice thickness = 1 mm, number of slices = 124), using an identical orientation as the functional images.

2.4. Psychophysiological interactions (PPI)

A traditional fMRI analysis was first carried out on the combined data from the two runs, using a covariate of no interest to identify the transition between runs (Bitan et al., 2006; Bitan et al., 2005; L. Liu et al., 2010). Parameter estimates of the hemodynamic response to three physiological conditions were created, namely the lexical condition (including all combinations of orthographic and phonological similarity), the perceptual condition (including both simple and complex controls), and the null condition (fixation).

The V1 seed region for PPI analysis was created for each individual in a 2-stage process. The activation maximum within the left cuneus was first identified from random effects group analysis for the 'spelling-simple' contrast. Although V1 was not mapped physiologically in the current study, the group maximum [-6 , -78 , 12 in MNI coordinates] lay within the dorsal bank of the calcarine sulcus, well within the boundaries of V1 as shown by previous studies (Dougherty et al., 2003; Sereno et al., 1995). The activation maximum that was closest to this group maxima was then identified for each individual. A 5mm radius sphere surrounding the individual maxima was used as the putative V1 seed region.

Using a ventral stream mask (ventral occipital, lingual gyrus, inferior temporal, and fusiform gyrus as delineated by the WFU Pickatlas toolbox for SPM), functional connectivity from the V1 seed region was estimated for each physiological condition (lexical, perceptual, and fixation). A psychophysiological interaction (PPI) term was then created to identify where functional connectivity during the lexical condition was greater than the perceptual condition (each contrasted to fixation). The global maximum in the PPI analysis was identified using a threshold of $p = 0.05$ (uncorrected for multiple comparisons); individuals who failed to show any PPI connectivity at this threshold were treated separately as a group with "no connectivity" during group analyses. (This threshold was not corrected for multiple comparisons because the objective was to find the one location with maximal connectivity within the ventral stream.) The x-, y-, and z-coordinates of the global maxima PPI connectivity were analyzed to determine whether the location of strongest connectivity changed systematically with subject age, sex, or standardized test scores. Multiple regression analysis tested the hypothesis that a combination of the factors (sex, age in

months, and standardized scores for verbal IQ, word reading accuracy or nonword reading accuracy) was significantly correlated to the x-, y-, or z-coordinate of the PPI connectivity maxima.

The interaction of these factors was examined in a series of ANOVAs. To create discrete groups, groups with high or lower verbal abilities were created for boys ($n=18$) and girls ($n=18$) based upon a median split of their verbal IQ scores. The high-skill group scored better than the population norm (verbal IQ > 116 with a mean = 128.9 ± 10.2 for boys and 124.8 ± 8.5 for girls); the lower-skill group was near the population norm (mean verbal IQ = 102.8 ± 10.0 for boys and 107.6 ± 6.5 for girls). Each skill group was further divided into younger (ages 9 through 11) and older subjects (ages 13 through 15). A 2-way ANOVA examined the effects and interaction of sex on the x-, y-, or z-coordinate of the PPI connectivity maxima for four subgroups (high-skill young [5 girls, 6 boys], high-skill old [3 girls, 4 boys], mid-skill young [2 girls, 4 boys], and mid-skill older subjects [8 girls, 4 boys]). Subsequent ANOVAs examined the specific interaction between sex and age within each skill group.

To visualize the effect of each factor on maxima position, the spatial coordinate (x, y, or z) was plotted as a function of age in each of four groups (high-skill girls, mid-skill girls, high-skill boys, and mid-skill boys). Results from different groups were combined in plots on graphs and a normalized brain to illustrate differences in maxima location between groups. In addition, a composite map was plotted as a function of the youngest age group that produced significant PPI connectivity ($p < 0.01$ for an individual, uncorrected for multiple comparisons). This map served two purposes. First, because mapping was based solely on age (by incorporating the connectivity map from every individual), this composite map identified maturational (age-related) effects for the subject pool that did not depend on sex or IQ. Second, this mapping confirmed that spatial shifts in PPI connectivity associated with age were not limited to the maxima.

3. Results

Left hemisphere

During the orthographic comparison task, 36 of 42 subjects (86%) showed significant V1 connectivity (i.e., psychophysiological interactions from the V1 seed region) within the ventral visual stream mask. Subjects with V1 connectivity had significantly better language and reading skills than those who did not (i.e., those seven subjects without significant PPI connectivity), showing higher verbal IQ and better word identification (Table 1); this group difference was strongest for the vocabulary subtest of the verbal IQ measurement ($t=3.514$, $p=.001$). Despite these differences in language skills, no difference was observed on accuracy during performance of the experimental task (93.2% vs. 91.9% on visual spelling, $t=0.64$, $p=.48$).

For those showing V1 connectivity, the position of the PPI maxima along the y-axis was significantly correlated to verbal IQ, age, and sex (multiple regression analysis, $F[3,32]=3.464$, $p=.028$). Among girls, the position of PPI maxima was also correlated with verbal IQ and age along the x-axis ($F[2,15]=3.863$, $p=.044$). No such effects were observed when age and sex were evaluated with word accuracy scores ($F[3,32]=1.954$, $p=.141$ for the x-axis; $F[3,32]=1.848$, $p=.185$ for the y-axis; $F[3,32]=1.430$, $p=.252$ for the z-axis) or with nonword accuracy scores ($F[3,32]=1.615$, $p=.205$ for the x-axis; $F[3,32]=1.180$, $p=.333$ for the y-axis; $F[3,32]=0.256$, $p=.856$ for the z-axis).

An ANOVA demonstrated different effects of verbal abilities (high or lower verbal IQ), sex, and age (young or old) on different coordinates. The x-coordinate showed a main effect of

sex ($F[1,28]=5.525$, $p=.026$) and an interaction of sex with the age/IQ groups ($F[7,28]=2.450$, $p=.043$); after accounting for sex, there was no significant differences between the age/IQ groups ($F[3,28]=1.172$, $p=.338$). The y-coordinate also showed main effects of sex ($F[1,28]=4.319$, $p=0.047$) and an interaction of sex with the age/IQ groups ($F[3,28]=3.564$, $p=.027$); after accounting for sex, there were also differences between the age/IQ groups ($F[3,28]=4.307$, $p=.013$). The z-coordinate was affected by differences between the age/IQ groups ($F[3,28]=4.977$, $p=.007$), interacting with sex ($F[3,28]=3.291$, $p=.011$). Because it was strongly correlated with the y- (but not x-) coordinate for both girls ($r = -.779$, $p < .001$) and boys ($r = -.871$, $p < .001$), no further analysis was done for the z-coordinate, as changes in the Y/Z plane reflect the tilt of the brain relative to the MNI coordinate system.

Graphs and overlays illustrate how the combination of verbal IQ, age, and sex affected the spatial location of V1 connectivity maxima. Figure 1 shows the effect of sex and age on maxima position among high verbal IQ subjects. The *medial* boundary of maxima is shown for girls at the left (vertical white line aligned across axial brain slices, x-coordinate = -39). The maxima of all other girls were lateral to this position, compared to 33% (3/9) for boys. The *anterior* boundary is shown for boys at the top and right (horizontal white line on axial slices at top and vertical white line on sagittal slices at right, y-coordinate = -45). The maxima of all other boys were posterior to this position, compared to 13% (1/8) for girls. Boys' maxima lie predominantly within inferior occipital cortex, whereas girls' maxima lay predominantly within inferotemporal and fusiform cortex (see sagittal sections at right).

Among high verbal IQ subjects, the trendline shows that maxima positions tend to shift laterally with age, although the correlation is small and not statistically significant for girls (slope = -2.2 mm/year, $r = -.459$, $p = .126$) or boys (slope = -1.5 mm/year, $r = -.255$, $p = .254$). The trendline shows that maxima positions also tend to shift posterior with age in these subjects (bottom), although this correlation is also not statistically significant for girls (slope = -6.2 mm/year, $r = -.600$, $p = .059$) or boys (slope = -3.6 mm/year, $r = -.377$, $p = .158$).

Figure 2 shows a different pattern for lower IQ subjects; white lines are in the same positions as boundary lines in Figure 1. Unlike high-IQ subjects, the proportion of medial maxima is 50% for both girls and boys (relative to white line, left axial series). Unlike high-IQ subjects, the proportion of anterior maxima was also similar for girls and boys (70% for girls and 75% for boys are anterior to the white line in top axial and right sagittal series). The effect of age differed for the two sexes. The lateral shift with age is significant for girls (slope = -5.0 mm/year, $r = -.726$, $p = .009$) but not boys (slope = -1.0 mm/year, $r = -.154$, $p = .357$); by contrast, the posterior shift with age is significant for boys (slope = -10.7 mm/year, $r = -.675$, $p = .033$) but not girls (slope = -6.20 mm/year, $r = -.600$, $p = .059$).

For those subject groups that showed significant correlations with a maxima coordinate, Figure 3 directly compares maxima location between high- vs. mid-skill subjects. In younger children, maxima of mid-skill girls are more medial than those of high-IQ girls, but as noted for Figure 2, the maxima in mid-skill girls show a significant *lateral* shift with age. Although the trendlines for the two groups nearly converge by age 15, the x-coordinate among mid-skill older girls (age 13) remains marginally more medial ($t = 1.971$, $df = 9$, $p = .080$). In younger children, maxima of mid-skill boys are anterior to those of high-IQ boys (ages 11, $t = 6.152$, $df = 8$, $p < .001$), but as noted for Figure 2, the maxima in mid-skill boys show a significant *posterior* shift with age. Among older boys (age 13), the y-coordinate in mid-skill subjects nonetheless remains marginally more anterior ($t = 2.232$, $df = 5$, $p = .076$). These results indicate a similar *effect of IQ* on connectivity maxima in boys and girls, with a shift in location delayed by age among mid-skill subjects; i.e., the maxima

location in the younger subjects has not yet shifted, with the shift instead occurring during maturation. The *effect of sex* on connectivity maxima is the direction of this shift, namely, lateral among girls and posterior among boys.

In order to isolate the effect of age on location, connectivity maps from all individuals at each age were merged (ages 9, 11, 13, or 15 years), then combined in a composite map. Figure 4 maps the earliest age at which PPI connectivity appeared. For the group, the area of PPI connectivity shifts progressively to age 13 in the directions predicted by the shifts in maxima location -- i.e., laterally within the temporal lobe ("L") and posterior from the fusiform gyrus into inferior occipital cortex ("P"). Additionally, a small area of PPI connectivity expands with age in anterior inferotemporal cortex ("A"). Because it was created to show the earliest age where connectivity appeared, regardless of whether older children also show connectivity at the same location, this map cannot differentiate between *shifts* in the location versus *expansion* in the area of connectivity. As a composite from all individuals in each age group, however, this map shows that the location of significant V1 connectivity depends partly on maturational development -- i.e., regardless of a child's sex or verbal IQ, V1 connectivity in posterior areas ("P"), lateral areas ("L"), or anterior areas ("A") did not appear in the population until children reached the appropriate age. Such maturational changes in the area of connectivity had nearly ceased by the age of 15.

Right hemisphere

During the orthographic comparison task, 30 of 42 subjects (71%) showed significant V1 connectivity within the ventral visual stream mask. The language and reading skills of subjects with and without V1 connectivity in the right hemisphere did not significantly differ (see Table 2).

For those showing V1 connectivity, the position of the PPI maxima was not significantly shifted by verbal IQ, age, or sex (multiple regression analysis, $F[3,31]=0.569$, $p=.640$ for x-axis; $F[3,31]=1.514$, $p=.230$ for y-axis; $F[3,31]=0.401$, $p=.754$ for z-axis), nor did the position shift with word reading accuracy scores ($F[3,31]=0.309$, $p=.819$ for x-axis; $F[3,31]=1.227$, $p=.316$ for y-axis; $F[3,31]=0.118$, $p=.949$ for z-axis) or nonword reading accuracy scores ($F[3,31]=0.473$, $p=.704$ for x-axis; $F[3,31]=1.241$, $p=.312$ for y-axis; $F[3,31]=0.512$, $p=.677$ for z-axis).

4. Discussion

This study demonstrated a maturational shift in the location of psychophysiological interactions (connectivity) from primary visual cortex (V1) to the left ventral occipitotemporal cortex among children making spelling judgments about written words. This shift in location was related not only to the age of the child, but also the child's sex and verbal abilities (as measured by verbal IQ). Furthermore, V1 connectivity in the left hemisphere and its location was shown to be important for strong language skills; children who showed significant V1 connectivity had higher verbal IQ and word identification scores than those who did not, and children with higher verbal IQ showed a shift in the location of connectivity at an earlier age.

The observed shift in V1 connectivity depended on a combination of factors that varies between individuals (age, verbal IQ, and sex). Individual variability in the *intensity* of brain activation (Demb, Boynton, & Heeger, 1997; Desroches et al., 2010; Hester, Fassbender, & Garavan, 2004; Newman, Carpenter, Varma, & Just, 2003; Osaka et al., 2004) and connectivity have previously been reported (Gianaros et al., 2008; Koyama et al., 2011; Maguire, Vargha-Khadem, & Mishkin, 2001; Mennes et al.; Seeley et al., 2007; Wager, Jonides, Smith, & Nichols, 2005), but variability in location is traditionally assumed to be

trivial, with group effects identified from voxel locations where all subjects show increased activation (or connectivity). This is the first study to demonstrate systematic variability in the *location* of connectivity, suggesting that *spatial* analysis of individual variability can improve our understanding of cognitive processing. Rather than examining developmental changes in connectivity strength (which might occur in any visual area that acquires responsivity to lexical stimuli), our findings were demonstrated by examining the influence of experimental variables on the location of maximal task-specific connectivity. This approach allows us to identify connectivity most directly related to task performance; these connections are likely to be most sensitive to subtle changes in development and performance. Just as hemispheric dominance for language increases during development (Everts et al., 2009; Spironelli & Angrilli, 2009), this systematic shift in the location of connectivity was only observed in the left hemisphere.

Recent studies have demonstrated that connectivity between the Visual Word Form Area and parietal areas involved in phonology are present in normal children but diminished or absent in dyslexic children (Horwitz et al., 1998; Ligges et al., 2010; Pugh et al., 2000; van der Mark et al., 2011). Although our subjects were within the normal range of language function, our study similarly shows an absence of language-specific connectivity from V1 to ventral occipitotemporal regions in children with lesser language skills. When present, our V1 connectivity results likely reflect the earliest lexical influence on visual processing, perhaps reflecting acquired stimulus specificity for letters, syllables, or words (Dehaene et al., 2010). The absence of lexical specificity within the visual system could help explain the deficit in connectivity and phonological processing in lower functioning children such as dyslexics; a word-related signal must be present within the visual system before it can be converted to phonology. This could explain why reading problems is the dominant characteristic of dyslexia (Frith, 1999; Lyon, Shaywitz, & Shaywitz, 2003), as phonological processing deficits by themselves should equally affect perception of spoken words.

Although the relationship between connectivity and activation is indirect, our connectivity results are generally consistent with fMRI activation findings. Relative to fixation, activation from viewing words extends through much of the left ventral occipitotemporal cortex (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003; Vinckier et al., 2007), and the location of activation when matching letters strings is highly variable across individuals (James, James, Jobard, Wong, & Gauthier, 2005; Polk et al., 2002). Our connectivity maxima were similarly variable across individuals and scattered throughout the left ventral occipitotemporal cortex. Just as activation in the left occipitotemporal region increases during development through age twelve, then diminishes through age fifteen (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011), our composite connectivity map increased in area through age thirteen with no additional connectivity at age fifteen. Our methods of analysis, however, provide information about interactions between brain regions that cannot be fully equated with activation studies. A task-specific lexical influence on visual connectivity was identified in our youngest subjects, for example, whereas activation studies that used a false-font baseline did not show lexical activation in early readers (Turkeltaub et al., 2003). Without requiring this baseline condition to demonstrate lexicality, our approach demonstrates a changing relationship between activity in V1 and another ventral stream area when viewing visually-presented words.

Previous activation studies have demonstrated a posterior-to-anterior progression within extrastriate, fusiform and inferotemporal cortices for visual processing of letters, syllables, and whole words (Cohen, Henry et al., 2004; Cohen et al., 2002; Dehaene et al., 2004). Our anterior-to-posterior progression of PPI connectivity with age suggests that lexical processing in visual cortex begins with larger graphemes in younger children and progressively involves smaller graphemes with maturation. Although counter-intuitive, this

is consistent with behavioral studies that show young children initially identify words from the visual configuration of the entire word, relying more on the spelling and phonetics as they grow older (Ehri, 1995; Ehri, 2005; Ehri & McCormick, 1998).

The posterior progression of PPI connectivity with age implies that selectivity is initially acquired through top-down influences on word recognition, rather than assembled through sublexical components. This is consistent with electrophysiological studies that show N1 acquires lexical tuning in the left occipitotemporal region as children begin to read (Maurer et al., 2007), as differentiation between meaningful words and letter strings requires cognitive knowledge of grapheme-word associations. Top-down modulation may explain why the position of connectivity within the ventral stream was correlated with verbal IQ rather than standardized measures of reading skill; verbal IQ measures the ability to apply knowledge of word similarities and vocabulary acquired through experience, abilities known to interact with reading comprehension and orthographic knowledge (Ehri & Rosenthal, 2007; Ricketts et al., 2007). Top-down influences while learning to read may permanently change how the visual system processes lexical stimuli, however, as subliminal word priming effects in the ventral occipitotemporal cortex of adults indicate a lexical component free of top-down effects (Kouider, Dehaene, Jobert, & Le Bihan, 2007). Our psychophysiological interactions on connectivity from V1 likely represent the earliest top-down influence of linguistic processes on bottom-up visual processing.

Shifts in PPI connectivity associated with age and verbal IQ were both in the same direction, whereas children who did not show any PPI connectivity showed the lowest verbal IQ and word recognition scores. This may indicate that language skills reflect the maturation of the brain; children who have not yet developed this PPI connectivity have relatively poor verbal IQ and word recognition scores, those with anteromedial PPI connectivity have intermediate verbal abilities (i.e., verbal IQ near the population norm), and those with shifted PPI connectivity have the best verbal abilities (verbal IQ better than the population norm). A high verbal IQ may thus reflect precocious development in the language system. Maturation changes could help explain linguistic differences between girls and boys, since girls in this age range are developmentally advanced (Giedd et al., 2006) and show greater language skills (Bornstein et al., 2004; Fenson et al., 1994; Lynn, 1992; Mann et al., 1990; Martin & Hoover, 1987; Martins et al., 2005; Undheim & Nordvik, 1992). Alternatively, more experience with language may result in strategic changes in word processing that is reflected in V1 connectivity, with posterior progression with age and language skill resulting from analysis of smaller graphemes. Lateral visual areas in ventral occipitotemporal cortex also tend to be involved in smaller-grain analysis of visual space (Hasson et al., 2003; Lerner et al., 2003; Levy et al., 2001), so the lateral shift in PPI connectivity with age and skill may also represent a shift towards finer-grain analysis of graphemes. Interestingly, activation in lateral fusiform cortex has also been reported when subjects attend to specific letters within a word or letter string (Cohen, Jobert, Le Bihan, & Dehaene, 2004; Flowers et al., 2004; James et al., 2005). The posterior extrastriate and lateral fusiform shifts may both achieve the same effect but by different means; the posterior shift in extrastriate cortex PPI connectivity facilitates identification of word components, whereas the lateral shift in fusiform gyrus recognizes the holistic visual pattern (word form) by integrating more details requiring central vision.

The posterior shift within extrastriate occipital cortex was prominent among boys, whereas the lateral shift within the fusiform gyrus was more prominent in girls. Interestingly, these fusiform and extrastriate visual areas reflect the regions whose activity is correlated with accurate visual-language performance in girls and boys, respectively (Burman et al., 2008). In their study, Burman and colleagues reported differences in language skills and brain activation across language tasks, but suggested that these might reflect developmental

differences that disappear by adulthood. If so, the lateral and posterior shifts for both sexes should both converge at maturation. Although this was the case for mid-skill children (i.e., those whose verbal IQ were near the general population norm of 100), it was not the case for children with high IQs. Expansion in the area of PPI connectivity had essentially ended by age 13, yet the location of maxima for high-IQ girls and boys remained separate; girls' maxima were lateral within the fusiform gyrus, whereas boys' maxima were posterior in extrastriate cortex. In addition to performance differences (Coney, 2002; Crossman & Polich, 1988), sex-related differences in brain activation (Baxter et al., 2003; Clements et al., 2006; Coney, 2002; Garn, Allen, & Larsen, 2009; Gauthier, Duyme, Zanca, & Capron, 2009; Harrington & Farias, 2008; Jaeger et al., 1998; Petrek, 2004; Pugh et al., 1996; Ragland, Coleman, Gur, Glahn, & Gur, 2000) and laterality (Baxter et al., 2003; Clements et al., 2006; Coney, 2002; Frost et al., 1999; Jaeger et al., 1998; Kansaku, Yamaura, & Kitazawa, 2000; Rossell, Bullmore, Williams, & David, 2002; Shaywitz et al., 1995) have been reported in adults, but are controversial (Allendorfer et al., 2011; Brickman et al., 2005; Buckner, Raichle, & Petersen, 1995; Frost et al., 1999; Garn et al., 2009; Gur et al., 2000; Haut & Barch, 2006; Hund-Georgiadis, Lex, Friederici, & von Cramon, 2002; Kherif, Josse, Seghier, & Price, 2009; Knecht et al., 2000; Papanicolaou et al., 2006; Roberts & Bell, 2002; Schlosser et al., 1998; Sommer, Aleman, Bouma, & Kahn, 2004; Wallentin, 2009; Weiss et al., 2003; Xu et al., 2001). Our findings suggest that sex differences in adults may depend on their verbal abilities, with greater differences appearing among highly skilled individuals. Such an interaction between sex and verbal fluency has been reported in visual and language areas (Gauthier et al., 2009).

5. Summary and conclusions

V1 psychophysiological interactions associated with a visual orthographic comparison task was used to identify the earliest linguistic influences in the visual pathway. The location of these interactions varied within the left occipitotemporal cortex, depending on verbal abilities (as measured by verbal IQ), age, and the sex of the individual. Maturation-related changes moved the area of maximal PPI connectivity towards regions associated with greater linguistic ability; this shift was predominantly lateral within the fusiform gyrus among girls, but predominantly posterior within the extrastriate occipital cortex among boys. Our findings indicate that individual variability in the location of connectivity can be meaningful, and suggest that different strategies between high-functioning girls and boys for performing linguistic tasks may persist into adulthood.

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- lexical task-dependent connectivity examined in ventral visual stream
- location of connectivity maxima varies systematically by age, sex and verbal IQ
- increases in age and verbal IQ produced similar shifts in maxima location
- lateral shift in temporal lobe for girls, posterior occipital shift for boys
- area of connectivity expands with age

Figure 1.

Age-related shifts in PPI maxima among boys and girls with high verbal IQ. Axial brain series along the left are aligned at the medial boundary of maxima locations among girls (white line, x-coordinate = -39); axial series along the top and the sagittal series at the right are aligned at the anterior boundary of maxima locations among boys (white line, y-coordinate = -45). Top and bottom graphs map maxima changes in x- and y-coordinates, respectively, as a function of age; relative age is color-coded as youngest (yellow for girls, cyan for boys), middle (pink for girls, purple for boys), and oldest (red for girls, dark blue for boys). Among higher-IQ children, girls' maxima tend to be lateral and anterior to those of boys, with the maxima for both sexes shifting lateral and posterior with age.

Figure 2.

Age-related shifts in PPI maxima among mid-skill boys and girls. Brain slices are aligned at the same locations as in Figure 1 (white line at x-coordinate = -39 in axial series along the left, white line at y-coordinate = -45 for others). Top and bottom graphs map maxima changes in x- and y-coordinates, respectively, as a function of age; relative age is color-coded as in Figure 1. Among mid-skill children, maxima location in the brain are intermixed for girls and boys; a lateral shift with age is greater for girls, whereas a posterior shift with age is greater for boys.

Figure 3.

PPI maxima location in children with high vs. midrange verbal IQ. **A**, maxima of girls with midrange verbal IQ are medial and shift laterally at a later age compared to those of girls with higher verbal IQ. **B**, maxima of mid-skill boys are anterior and shift posterior at a later age compared to boys with high-skill boys. Mid- and high-skill categories are based upon a median split of verbal IQ scores (median is 116 for girls and 117 for boys).

Figure 4.

V1 connectivity map showing incremental expansion in region of PPI connectivity with age. The earliest age (in years) at which PPI connectivity appeared is color-coded; red = 9, green = 11, blue = 13, and yellow = 15. Up to the age of 13, the area of PPI connectivity expands incrementally with age, progressing from the fusiform gyrus posterior into occipital cortex ('P') and lateral into inferotemporal cortex ('L'). The area of connectivity also expands with age in anterior inferotemporal cortex ('A').

Handedness and language skills among subjects who did and did not show task-specific connectivity from V1 in the left hemisphere.

Table 1

TEST	PPI connectivity		No connectivity		Difference t-value	Difference p-value
	mean	SE	mean	SE		
handedness (Likert scale)	78.2	2.03	81.4	3.89	0.715	.479
Verbal IQ (WASI)	116.3	2.34	101.7	3.03	3.235	.002 *
Word Attack (WJ-III)	107.2	1.64	104.1	3.69	0.729	.470
Word ID (WJ-III)	112	1.6	101.6	2.62	2.899	.006 *
Spelling (WRAT)	114.4	1.91	105.7	3.26	1.191	.240

* p<.05 using a 2-tailed t-test

Handedness and language skills among subjects who did and did not show task-specific connectivity from V1 in the right hemisphere.

Table 2

TEST	PPI connectivity		No connectivity		Difference t-value	Difference p-value
	mean	SE	mean	SE		
handedness (Likert scale)	76.7	2.30	82.9	2.50	1.822	.076
Verbal IQ (WASI)	112.6	2.74	118.2	3.34	1.285	.206
Word Attack (WJ-III)	105.5	1.72	110.0	3.07	1.253	.217
Word ID (WJ-III)	108.9	1.85	113.7	2.71	1.429	.161
Spelling (WRAT)	112.0	2.13	115.2	3.28	0.802	.428