Dyslexic children lack word selectivity gradients in occipito-temporal and inferior frontal cortex

O.A. Olulade, D.L. Flowers, E.M. Napoliello, G.F. Eden*

Center for the Study of Learning, Georgetown University Medical Center, Washington, DC, USA

ABSTRACT

fMRI studies using a region-of-interest approach have revealed that the ventral portion of the left occipito-temporal cortex, which is specialized for orthographic processing of visually presented words (and includes the so-called "visual word form area", VWFA), is characterized by a posterior-to-anterior gradient of increasing selectivity for words in typically reading adults, adolescents, and children (e.g. Brem et al., 2006, 2009). Similarly, the left inferior frontal cortex (IFC) has been shown to exhibit a medial-to-lateral gradient of print selectivity in typically reading adults (Vinckier et al., 2007). Functional brain imaging studies of dyslexia have reported relative underactivity in left hemisphere occipito-temporal and inferior frontal regions using whole-brain analyses during word processing tasks. Hence, the question arises whether gradient sensitivities in these regions are altered in dyslexia. Indeed, a region-of-interest analysis revealed the gradient-specific functional specialization in the occipito-temporal cortex to be disrupted in dyslexic children (van der Mark et al., 2009). Building on these studies, we here (1) investigate if a word-selective gradient exists in the inferior frontal cortex in addition to the occipito-temporal cortex in normally reading children, (2) compare typically reading with dyslexic children, and (3) examine functional connections between these regions in both groups. We replicated the previously reported anterior-to-posterior gradient of increasing selectivity for words in the left occipito-temporal cortex in typically reading children, and its absence in the dyslexic children. Our novel finding is the detection of a pattern of increasing selectivity for words along the medial-to-lateral axis of the left inferior frontal cortex in typically reading children and evidence of functional connectivity between the most lateral aspect of this area and the anterior aspects of the occipito-temporal cortex. We report absence of an IFC gradient and connectivity between the lateral aspect of the IFC and the anterior occipito-temporal cortex in the dyslexic children. Together, our results provide insights into the source of the anomalies reported in previous studies of dyslexia and add to the growing evidence of an orthographic role of IFC in reading.

1. Introduction

Developmental dyslexia is a common learning disability characterized by impaired reading accuracy and/or fluency. It is often accompanied by difficulties in spelling, and because of reduced reading experience, usually leads to a limited sight word vocabulary and poor reading comprehension (Lyon et al., 2003). Dyslexia is prevalent in many cultures, even though the formal diagnosis and some of the cardinal features vary depending on the language and the orthography used. For instance, while reading accuracy is often the preferred diagnostic measure for dyslexia in English-speaking countries, the rate of reading as well as spelling skills are often used to characterize dyslexia in languages with a shallow orthography such as German (see Erickson and Sachse, 2010). Importantly, independent of the spoken languages and writing systems used, it has now been shown that dyslexia exists worldwide, has a neurobiological origin, and is highly heritable (Peterson and Pennington, 2012).

Evidence from behavioral studies of dyslexia has demonstrated that weaknesses in phonological processing represent the core deficit of the reading difficulties (Wagner and Torgesen, 1987; Bruck, 1992; Stanovich and Siegel, 1994; Morris et al., 1998). In the last two decades, neuroimaging studies comparing dyslexic and typical readers have revealed differences in brain activity in left hemisphere language regions; some of these have been posited to be involved in phonological processing, including inferior frontal and parieto-temporal cortices (for reviews, see Pugh et al., 2001; Démonet et al., 2004; Maisog et al., 2008; Richlan et al., 2009; Richlan et al., 2013; Richlan, 2012). Most of these studies have also identified between-group differences in the left ventral occipito-temporal cortex (OTC) (Salmelin et al., 1996; Rumsey

* Correspondence to: Center for the Study of Learning, Department of Pediatrics, Georgetown University Medical Center, Building D, Suite 150, 4000 Reservoir Road NW, Washington, DC 20057, USA. Tel.: 202 687 6893; fax: 202 784 2414.

E-mail address: oao24@georgetown.edu (O.A. Olulade), lflowers@triad.rr.com (D.L. Flowers), emn5@georgetown.edu (E.M. Napoliello), edeng@georgetown.edu (G.F. Eden).

et al., 1997; Brunswick et al., 1999; Paulesu, 2001; Shaywitz et al., 2002; Cao et al., 2006; Maurer et al., 2007; Olulade et al., 2012; Richlan et al., 2011). This region has been of considerable interest in reading research because it encompasses the so-called "visual word form area" (VWFA (Cohen et al., 2000; Cohen et al., 2002; McCandliss et al., 2003; Cohen and Dehaene, 2004)). The VWFA is thought to be involved in fast ortho-graphic processing of visually presented familiar words or letter strings (Salmelin et al., 1996; Cohen et al., 2002; Petersen et al., 1990; Tarkiainen et al., 1999; Dehaene et al., 2004; Maurer et al., 2006; Baker et al., 2007). It has been suggested that differences observed in the VWFA between dyslexics and controls are secondary in their devel-opmental onset to the phonological weakness attributed to altered parieto-temporal and inferior frontal function (Pugh et al., 2001; McCandliss and Noble, 2003). However, a recent study reported the OTC as the only area underactivated in dyslexics compared with non-dyslexics in meta-analyses conducted in children as well as in adults. This indicates early and persistent involvement of the OTC in dyslexia (Richlan et al., 2011). Further, in a study combining dyslexic groups of participants from three countries, the left OTC was identified as the only region to be underactivated when compared with the control groups (Paulesu, 2001).

Most neuroimaging studies published to date have searched for the most salient differences between groups of dyslexics and their typically reading counterparts by conducting whole-brain analysis to identify ac-tivity underlying reading or reading-related skills, then reporting on between-group differences. However, other experimental and analytic approaches have been used to understand the functional neuroanatomy of reading and reading disability. One notable approach has been to ex-amine in detail pre-specified regions of the brain using a region-of-interest (ROI) analysis, and to examine gradient patterns (i.e. differen-tial task activations) amongst a series of ROIs. Specifically, the ventral OTC, often referred to as the "visual word form system" (VWFS), has been shown to demonstrate a posterior-to-anterior gradient of increas-ing word selectivity in typical readers. That is, in French-speaking adults (Vinckier et al., 2007) and in Swiss–German-speaking adults, adoles-cents (Brem et al., 2006; Brem et al., 2009), and children (Brem et al., 2009; van der Mark et al., 2009), as well as English-speaking adults and children (Olulade et al., 2013), investigators have observed a rela-tive signal increase for word stimuli compared to false-font/symbol-string stimuli along the posterior-to-anterior axis in the medial aspect of the left OTC, with the absence of this pattern reported in the right hemisphere homologue. These results demonstrate the presence of hi-erarchical specialization in a region of the brain that is important for or-thographic processing of visually presented words and automatic word recognition in individuals with typical reading skills. In a recent report (Olulade et al., 2013), we demonstrated developmental differences be-tween children and adults in the nature of this gradient, providing evi-dence of fine-tuning of functional specialization in the VWFS with age-dependent reading experience.

A critical question is whether this word-sensitive architecture in the ventral OTC is altered in individuals with dyslexia. This was addressed by van der Mark et al. (2009), who employed a region-of-interest anal-ysis involving a series of spheres within the left ventral OTC to examine activation in response to pseudoword, pseudohomophone, and real-word stimuli contrasted with false-font strings. The typically reading children exhibited significantly greater activation for false fonts relative to real words in the most posterior region, and significantly greater ac-tivation for real words relative to false fonts in an anterior region, there-by confirming the previously reported posterior-to-anterior gradient for proficient readers. Similar findings were observed for pseudowords, which yielded significantly greater activation than false fonts in the three most anterior regions. By contrast, the dyslexic children did not show this gradient of word selectivity. By moving beyond the simple ob-servation of hypoactivity in the occipito-temporal region, this approach has uncovered the complex nature of the differences that exist in dyslexia.

Several questions, however, remain unanswered. First, does the lack of a gradient in dyslexia in the VWFS also exist in children who read in English? The answer to this question is important to our understanding of the universal versus orthography-specific aspects of dyslexia, as well as the role of the VWFS in reading generally. Based on current models of reading in different orthographies, one would anticipate disruption of the gradient in dyslexic readers of English. Specifically, it has been sug-gested that for orthographies where there is less (e.g. English) or no (e.g. Chinese) grapheme–phoneme correspondence, there is greater re-liance on the OTC and IFC (Richlan, 2014). Research in alphabetic lan-guages indicates greater engagement of the OTC and the inferior frontal gyrus (IFG) by readers of English, which has a "deep" orthogra-phy, whereas readers of Italian, which is "shallow," preferentially en-gage the posterior superior temporal gyrus (Paulesu et al., 2000). For shallow languages, which includes German, the mapping between graphemes and phonemes is one-to-one, while reading in English re-quires more words to be recognized by sight (i.e. words with irregular spelling), placing greater reliance on the VWFA. We therefore fully ex-pected to replicate the OTC disruption in dyslexic readers of English. A second question concerns the role of the IFG, which traditionally has been considered a contributor to phonological assembly and articulato-ry planning (Pugh et al., 2001). As such, it is surprising that Vinckier and colleagues found a gradient of increasing word selectivity not only in the OTC in typically reading adults, but also in Broca's area (Vinckier et al., 2007). This inferior frontal gradient occurred along the transverse axis, with selectivity for words increasing from medial to lateral ROIs. The authors postulated that co-occurrence of gradients of word selectiv-ity in the left inferior frontal cortex (IFC) region and in the VWFS may be a result of neuronal connections between left hemisphere posterior vi-sual (occipito-temporal) and anterior language regions, but did not test this hypothesis directly. Replication of a topographical organization in the left IFC, this time in a group of younger readers, would be impor-tant to establish whether there is a more direct orthographic role for the IFC in print processing, making it similar in function to the VWFA (Paulesu, 2001). In addition to examining the IFC in normally reading children, we also tested the integrity of this area in children with dyslex-ia. This builds on a body of literature that, generally speaking, has been mixed, with some reporting underactivity in the dyslexic group com-pared to the control group in the IFC (Cao et al., 2006; Brambati et al., 2006; Booth et al., 2007; Schulz et al., 2008) but others not (Brunswick et al., 1999; Shaywitz et al., 1998; Georgiewa et al., 2002). As such, a more focused examination of the IFC region involving gradi-ent sensitivity can shed light on this issue. Finally, we examined func-tional connectivity between the left IFC and ventral OTC with the expectation that, as suggested by Vinckier et al. (2007), they are func-tionally connected in typical readers. In studies of dyslexia, several in-vestigators have reported altered connectivity between brain regions involved in the various aspects of word processing (Horwitz et al., 1998; Pugh et al., 2000; Stanberry et al., 2006; Cao et al., 2008; Ligges et al., 2010; van der Mark et al., 2011; Vourkas et al., 2011), including an observation of weaker connectivity between the VWFA and the IFG reported by van der Mark et al., (2011). Together, the results should ad-vance our understanding of the roles of the VWFA and IFG in readers of English, their interrelationship, and their functionality in children with dyslexia.

2. Materials and methods

2.1. Participants

All subjects were monolingual native speakers of English without prior diagnosis of developmental disability or psychiatric disorder. Sub-jects underwent a battery of behavioral tests to measure intelligence, reading proficiency, and skills known to support reading. The Wechsler Abbreviated Scale of Intelligence (WASI) was used to measure Verbal and Performance IQ (Wechsler, 1999). To be eligible for the study all

participants had to have a Full-Scale WASI IQ (FSIQ-4) standard score at or above 80. The children with dyslexia were recruited from a school that specializes in learning disabilities and had a documented history of underachievement in reading. They were selected to be in the study if their Woodcock–Johnson Tests of Achievement (WJ III) (Woodcock et al., 2001) Word Identification (WID) or WJ III Word Attack (WA) standard score was at or below 92, while the controls performed above a standard score of 92 on these measures of single real word and pseudoword reading. Controls were recruited from families with similar backgrounds and in close geographical proximity to the dyslexic children. Some of the same participants have been included in prior reports on reading (Olulade et al., 2013) and dyslexia (Evans et al., 2014a; Evans et al., 2014b; Krafnick et al., 2014; Krafnick et al., 2011).

We used the Lindamood Auditory Conceptualization Test—Third Edition (LAC-3) to assess phonological awareness (Lindamood and Lindamood, 2004) and the Rapid Automatized Naming (RAN) test to measure naming fluency for letters and numbers, as well as objects and colors (Denckla and Rudel, 1976a; Denckla et al., 1976b). Handedness was assessed via the Edinburgh Handedness Inventory (Oldfield, 1971). Table 1 contains mean group performance data on these behavioral measures, as well as subject demographic information for the twenty-eight children (12 controls, 16 dyslexics) included in the study.

As can been seen from Table 1, the groups were closely matched on verbal IQ (VIQ) and chronological age. The dyslexic group, compared with the controls, demonstrated significant weaknesses on measures of reading, phonological awareness, and rapid naming. Assent was obtained from each subject, and a legal guardian provided consent prior to the start of the study. All experimental procedures were approved by the Georgetown University Institutional Review Board.

2.2. fMRI task and data acquisition

Subjects completed an implicit word processing task (Olulade et al., 2013; Price et al., 1996; Turkeltaub et al., 2003; Turkeltaub et al., 2004) during the acquisition of fMRI data. This task involves the detection of a tall character within a visually presented real word (RW). Subjects responded by pressing a button in their right hand if an ascending feature was contained within the presented stimulus (e.g. 'h' in '**chess**'), and a button in their left hand if there was no ascender in the word (e.g. '**sauce**'). During this task, subjects are not required to explicitly read the presented word; however, reading occurs implicitly without conscious effort, and the resultant activation maps are comparable to those reported for studies that require aloud reading (Price et al., 1996). A specific advantage of this task for the current study is that it avoids between-group difference in task performance, which is difficult to avoid in studies of dyslexia using explicit word reading paradigms (and which contributes to uncertainty in the interpretation of the

Table 1
Subject demographics and behavioral scores.

	Controls	Dyslexics	p-Value
N	12	16	—
Sex (male/female)	6/6	9/7	—
Age (yrs)	10.1 ± 2.9	10.0 ± 2.1	n.s.
Handedness	77.5 ± 58	73.4 ± 51	n.s.
Verbal IQ	116 ± 15	107 ± 10	n.s.
Real word reading	116 ± 12	77 ± 11	$p < 0.0001$
Pseudoword reading	112 ± 11	87 ± 12	$p < 0.0001$
Phonological awareness	114 ± 14	93 ± 10	$p < 0.0001$
Naming of letters & numbers	107 ± 20	80 ± 13	$p < 0.001$
Naming of colors & objects	100 ± 21	86 ± 15	$p < 0.05$

Mean standard scores and corresponding standard deviations are presented for each group: Handedness (Edinburgh Handedness Inventory), verbal IQ (Wechsler Abbreviated Scale of Intelligence), single real word and pseudoword reading (Woodcock—Johnson III Tests of Achievement), phonological awareness (Lindamood Auditory Conceptualization Test, 3rd Ed.) and rapid naming (Rapid Automatized Naming) for letters and numbers as well as colors and objects. n.s.: non-significant.

resultant activation maps). A block-design paradigm was utilized, and blocks with RW stimuli alternated with blocks of false-font (FF) strings and blocks of a baseline fixation condition (Fix). The false-font stimuli were utilized as an active control condition and were matched to the word stimuli for visual characteristics such as size, number of characters, and location of ascenders and descenders. During the fixation blocks, a cross hair was displayed in the center of the screen, and the children were instructed to fixate on the cross hair and rest.

Stimulus presentation, image acquisition, and analyses were the same as described in our previous study comparing typically reading children and adults on this task (Olulade et al., 2013). Specifically, each subject completed two runs, with each run consisting of two blocks of each condition (i.e. RW or FF; 10 stimuli per block). For each trial within an RW or FF block, the stimulus was presented for 1.2s, followed by a fixation cross hair for 3 s. RW or FF blocks lasted 42 s, while the intervening Fix blocks lasted for 18 s, and as such, the overall duration (and number of brain volumes acquired; $n = 28$ time-points per run) was the same for each of the three conditions. The length of each run was 4 min and 27 s. Subjects were instructed to respond as quickly as possible during the trial period. For both stimulus categories, characters were displayed in black on a white background. Both runs were included in the analysis for each subject. Stimulus presentation and recording of responses were controlled using the Presentation software (Neurobehavioral Systems Inc, Albany, CA, USA). All subjects underwent a training session in a mock scanner prior to the experiment to familiarize them with the MRI environment, and to minimize the potential for motion artifacts.

All data were acquired on a 3 T Siemens Trio scanner located in the Center for Functional and Molecular Imaging at the Georgetown University Medical Center, Washington, DC. Eighty-nine images consisting of 50 contiguous axial slices covering the whole brain were acquired within each functional run using a standard echo-planar imaging sequence and the following parameters: FOV = 192 mm, slice thickness = 2.8 mm (0.2 mm inter-slice gap), in-plane resolution = 64 × 64 (voxel size = 3 mm isotropic), flip angle = 90°, TE = 30 ms, TR = 3 s.

2.3. Functional data analysis

Datasets were pre-processed and analyzed using SPM8 (http://fil.ion.ucl.ac.uk/spm/). After the first five scans in each run were discarded (to avoid T_1 saturation effects), all datasets were motion corrected, normalized to the Montreal Neurological Institute (MNI) EPI template, resampled to 2 mm³ isotropic voxels, and smoothed with a Gaussian kernel of 8 mm full width at half maximum. Next, the datasets were scrutinized for head motion artifacts. Time-points for which the scan-to-scan motion was greater than a threshold of 1 mm (33% of the original voxel size) were identified and added as a regression parameter during statistical analysis so that they were excluded from the model, and thus would not contribute to the statistical maps. In addition, any subjects for whom more than 25% of the images in either run exhibited scan-to-scan motion above this threshold (1 mm) were completely excluded from further analysis. To ensure that the two groups entered into the final analysis did not differ on head motion, we compared the mean percentage of scans where motion exceeded the 1 mm threshold; there was no significant difference in this measure ($p > 0.1$).

Statistical analysis of the resulting datasets was performed in multiple steps. First, whole-brain activation maps were generated at the group level. This portion of the analysis was performed for consistency with previous studies examining functional selectivity within OTC (Brem et al., 2006; Brem et al., 2009; van der Mark et al., 2009; Olulade et al., 2013) and is described here to provide a context for the more detailed analysis on regional functional specializations as assessed by ROIs. Within- and between-group maps were generated for the real word and false-font conditions relative to baseline (i.e. RW vs. Fix; FF vs. Fix), and for the word-selective (between-condition: RW vs. FF) comparison. Next, gradient maps of differential activity between real

words and false-fonts were generated in each group for visualization of potential gradients of word-selectivity in the occipito-temporal and inferior frontal regions. Then, region-of-interest analysis was performed in these same areas to statistically test for differences between dyslexic and typical readers. All of these procedures follow the same methods as those described in our previous study (Olulade et al., 2013) and were similar to analytic approaches of previous publications (e.g. Vinckier et al., 2007; van der Mark et al., 2009)). Finally, we examined functional connectivity between these regions under conditions of real word processing. More detailed information about the procedures employed in each step is presented next.

2.3.1. Whole-brain activation maps

At the first level of analysis, single-subject statistical parametric maps were generated for each of the active task conditions relative to fixation (i.e. *RW* vs. *Fix* and *FF* vs. *Fix*), and for the between-condition contrast (*RW* vs. *FF*) for each of the two groups (dyslexics and controls). The blood oxygenation level dependent (BOLD) response to the stimulus blocks was modeled using the canonical SPM hemodynamic response function. Functional datasets were high-pass filtered with a cut-off of 128 s and corrected for auto-correlations using an AR(1) model (Friston et al., 2002). For each of the defined conditions, within-group activation maps were generated using the subject-specific contrast images in a one-sample *t*-test. Significantly active clusters for *RW* vs. *Fix* and *FF* vs. *Fix* comparisons were considered to be those that survived a cluster-size whole-brain correction implemented using the CorrClusTh algorithm by Nichols at a cluster-defining threshold of $p < 0.001$. *RW* vs. *FF* maps were presented at an uncorrected threshold of $p < 0.001$ ($k > 20$), comparable to thresholds employed in other studies involving dyslexic individuals and/or children (Cao et al., 2006; van der Mark et al., 2009; Olulade et al., 2013; Brambati et al., 2006; Booth et al., 2001; Booth et al., 2004; Brown et al., 2005; Hoeft et al., 2007; Brem et al., 2010). Additionally, to test for regions that exhibited reliable differences between groups, two-sample *t*-tests ($p < 0.001$; minimum $k = 20$) were conducted at the second level for each of the three aforementioned contrasts.

2.3.2. Gradient images

Gradient images of differential activation between real words and false-fonts were generated for the purpose of visualizing the layout of spatial sensitivity to both categories of stimuli in the OTC and in the IFC. As in previous studies (Vinckier et al., 2007; van der Mark et al., 2009; Olulade et al., 2013), these images do not represent a statistical test for the gradient of increasing selectivity for words; this will be addressed in the subsequent analysis. Gradient images were generated using the fMRI within-group *t*-statistic (spmT) maps described in the previous section for the *RW* vs. *Fix* and *FF* vs. *Fix* conditions. Specifically, for each group, the aforementioned within-group maps were generated using an uncorrected threshold of $p < 0.005$ and saved as *t*-statistic images. Next, these fMRI *t*-statistic maps were loaded into Matlab (The MathWorks Inc., Natick, MA, USA), and the map for *FF* vs. Fix was subtracted voxel-wise from the map for *RW* vs. *Fix*. As such, for the resulting difference (gradient) map, voxels with *t*-statistic values greater than zero represent locations where significant activity for *RW*s was greater than significant activity for *FF*s, and voxels with values less than zero represent locations where it was the reverse. To aid visualization of the activation profiles, we masked the resulting gradient images to display activations only in occipito-temporal regions and inferior frontal regions. Masks were defined using MARSBAR (http://marsbar.sourceforge.net) and included fusiform, lingual, and inferior occipital gyri for the OTC, and pars triangularis and opercularis for the IFC.

2.3.3. Regions of interest

Region-of-interest analysis was used to statistically test for the gradient of increasing selectivity for real words in the VWFS and IFC. The procedures employed are detailed below for each region.

2.3.3.1. Occipito-temporal ROIs. Six non-overlapping, spherical ROIs were defined along the anterior-to-posterior axis of the left OTC to statistically test for a posterior-to-anterior gradient of increasing word selectivity for our groups of dyslexics and typical readers in this area. ROIs defined within this region encompassed the VWFA as well as locations anterior and posterior to it. The centers of the ROI spheres were chosen to sample occipito-temporal regions that most reliably exhibited activity related to the active conditions (i.e. real words and false-fonts), without bias towards a particular group (i.e. dyslexics or controls) or condition (Olulade et al., 2013). In this procedure, we first defined single-subject *Active Condition* vs. *Fix* maps by combining real word and false-font activations at the first level, and employed a one-sample *t*-test at the second level to combine the resulting activation maps over all twenty-eight children, thereby generating a single-group map defined at a height threshold of $p < 0.001$, *FWE*-corrected for cluster size. Next, the posterior half of the fusiform gyrus (as defined in the MARSBAR toolbox) was divided into subsections along the anteroposterior axis. These subsections were subsequently used as bounding boxes to locate six activation peaks within the aforementioned group map that were used as the centers of the ROI spheres. Each sphere had a radius of 4 mm and contained approximately 33 voxels. A further six spheres were placed at the same locations in the contralateral hemisphere to serve as a control (i.e. to validate the specificity of the results). For each subject, percent signal change was computed within the defined ROIs for the contrast of $RW-FF$, and these values were subsequently entered into an analysis of variance (ANOVA) for each hemisphere separately in two steps.

First we tested for a pattern representative of a gradient of increasing selectivity for words in the typical readers by subjecting values for this group to a one-way ANOVA (main effect of *ROI*), and then subsequently testing for a linear trend in the pattern of activation. This procedure was then repeated for the dyslexic group. Then, to statistically test for a difference between the dyslexics and typical readers in differential response patterns within the VWFS, we conducted a two-way repeated measures ANOVA using *ROI* as a within-subject factor and *Group* as a between-subject factor. For comparison with previous studies, we also separately examined activations for each condition relative to baseline in each group to determine whether any observed between-group activation differences were driven by the activations specific to the real words or false-fonts.

2.3.3.2. Inferior frontal ROIs. A similar procedure was used to define ROIs in bilateral inferior frontal regions, with the aim of examining whether a medial-to-lateral gradient of increasing word selectivity, previously demonstrated in typically reading adults (Vinckier et al., 2007), would be observed in typically reading children, and further, in dyslexic children. MARSBAR was used to divide portions of the inferior frontal region (specifically Broca's area, i.e. pars opercularis and pars triangularis) into sections along the transverse axis. Activation peaks within the previously described *Active Condition* vs. *Fix* group ($N = 28$) map were located within each of the bounding sections and used as centers of spherical ROIs with 4 mm radius. Five ROIs were selected in the left hemisphere, and another five were placed in contralateral homotopic locations in the right hemisphere, again serving as a control. As in the analysis for the OTC for the direct between-group comparison, $RW-FF$ percent signal change was obtained for each of the defined IFC ROIs, and resulting values were entered into a repeated measures ANOVA and also subjected to linear trend analysis. Similar to the OTC, we again separately examined activations for each condition relative to baseline for each group to determine the contribution of each condition to observed differences.

2.3.4. Connectivity analysis

Correlation analysis was performed to examine functional connectivity between left hemisphere occipito-temporal and inferior frontal regions during word processing. We specifically tested whether anterior (assumed to be selective for real words) but not posterior (assumed not

to be selective for real words) VWFS regions exhibited functional connectivity to lateral and medial inferior frontal regions, respectively, during real word processing. For both the typically reading and dyslexic children, we measured the average connectivity between the two most anterior ROIs in the VWFS and the two most lateral ROIs in the IFC. Similarly, we measured the average connectivity between the two most posterior ROIs in the VWFS and two most medial ROIs in the IFC. This approach was taken because our question pertained to the extremes of the gradients, and to increase statistical power. Connectivity between the aforementioned regions was measured using the method outlined by Fair et al. (2007). Correspondingly, excluding the first five scans of each run (to account for T_1 saturation effects), scans acquired during the RW condition were selected after allowing for hemodynamic delay and return to baseline. Only "steady-state" scans were used in analysis to avoid variance due to the increase in signal associated with the presence of a stimulus, and subsequent decrease following the removal of the stimulus. Steady-state was assumed to occur 9 s after the beginning of the first stimulus and decay was assumed to begin 3 s after the removal of the last stimulus. Over the two runs, 48 time-points were assigned to the RW processing condition. The average time-series within each of the regions was extracted for the time-points corresponding to this condition for each subject, and the pair-wise correlations were performed following detrending and bandpass filtering. The six rigid-body motion parameters, cerebrospinal fluid, and white matter signal were included as regressors to account for fluctuations unrelated to neural processes, including head motion and physiological artifacts. Resulting correlation coefficient values (r) were normalized via conversion to Fisher's z-scores (Silver and Dunlap, 1987) using the equation $[z = (n - 3)^{0.5} * 0.5 \times \log_e((1 + r) / (1 - r))]$ (n = number of subjects in group) (Hinkle et al., 2002) and averaged across the regions as previously specified. Subsequent values were averaged over all subjects in each group and tested for group significance via a one-sample t-test.

3. Results

3.1. In-scanner task performance

In-scanner task performance measures for both groups are presented in Table 2. Scores were entered into a 2-way repeated measures ANOVA with Group and Condition as fixed factors and Accuracy and Response Time as dependent variables. For Accuracy, there was no main effect of Group ($F(1,27) = 0.01$; $P = 0.93$) or Condition ($F(1,27) = 0.58$; $P = 0.45$), and no significant Group × Condition interaction ($F(1,27) = 0.06$; $P = 0.81$). For Response Time there was a significant main effect of Group ($F(1,27) = 6.08$; $P = 0.02$) as overall, the typical readers responded faster than the dyslexics. This effect was common to both conditions as no significant interaction ($F(1,27) = 0.33$; $P = 0.57$) emerged. There was no main effect of Condition ($F(1,27) = 0.0$; $P = 0.94$). Subjects in both groups performed with high accuracy on both the real word and false-font conditions. Additionally, there were no within-group differences in performance accuracy or reaction time between real words and false-fonts when assessed separately via two-tailed t-tests ($p > 0.05$), and importantly, no between-group differences were observed for the word-selective contrast of interest (i.e. RW−FF).

Table 2
Subject in-scanner performance.

	Controls	Dyslexics	p-Value
Accuracy (% correct)			
Real words	89.8 ± 14	90.8 ± 7.6	n.s.
False fonts	88.2 ± 12	87.8 ± 12	n.s.
RW/FF difference	1.58 ± 6.0	3.07 ± 11	n.s.
Response time (ms)			
Real words	915 ± 132	1043 ± 196	n.s.
False fonts	938 ± 122	1018 ± 137	n.s.
RW/FF difference	−23.0 ± 72	25.2 ± 85.5	n.s.

3.2. fMRI whole-brain group comparisons

Group-level, whole-brain statistical maps of activation were surface-rendered on the standardized SPM Montreal Neurological Institute (MNI) surface brain template and are presented in Fig. 1. The corresponding MNI coordinates for these activation peaks are reported in Table 3.

3.2.1. Control group

RW vs. Fix: As expected in the group of typical readers, real words when contrasted against the fixation baseline activated portions of what is considered the word-reading network. These areas included left occipito-temporal, parietal, and inferior frontal cortices. Left OTC included the fusiform gyrus, consistent with the description of the VWFS, and the location of the peak of activation was MNI coordinates (x, y, z) −38, −50, −24, close to the location reported for the VWFA (MNI: −43, −54, −17 (McCandliss et al., 2003)). Activation was also observed in the left cuneus, left parietal cortex, left precentral gyrus extending into the right hemisphere, and the left superior and inferior frontal gyri.

FF vs. Fix: False-fonts activated a large bilateral network in typical readers, with activations observed in bilateral occipital and parietal regions. Left medial frontal gyrus was also activated during this condition, as well as the right inferior frontal gyrus.

RW vs. FF: A direct contrast between the two conditions (i.e. RW vs. FF) revealed word-selective activation in two locations in the left hemisphere: the anterior fusiform gyrus (MNI: −40, −44, −18) and lateral inferior frontal gyrus (MNI: −50, 12, 24). In the right hemisphere, activation was observed in the inferior parietal lobule and in two locations within the superior temporal gyrus.

3.2.2. Dyslexic group

RW vs. Fix: The dyslexic children also activated portions of the reading network during real word processing, namely the left inferior frontal insula. However, no activation was observed close to the VWFA; instead, activations within the ventral visual cortex were restricted to posterior occipital areas. The RW vs. Fix contrast also revealed activation in the left cerebellum and left medial frontal gyrus, and in the right superior parietal lobule and right angular gyrus.

FF vs. Fix: False-font activations in the dyslexic group also included bilateral occipital, parietal, and medial frontal regions, similar to the typically reading group.

RW vs. FF: The word-selective contrast in the dyslexics revealed greater activation for words in bilateral posterior regions including occipital/lingual gyri and superior temporal gyri. Activation was also observed in the right supramarginal gyrus and precuneus. Notably, the dyslexics did not exhibit any activation in left occipito-temporal (i.e. where the VWFA is located) or inferior frontal regions for this contrast.

3.2.3. Between-group comparisons

RW vs. Fix: Between-group comparisons for the RW vs. Fix contrast revealed greater activation for the controls than dyslexics in the left fusiform (occipito-temporal) region. The peak of the activation cluster in the left OTC (MNI: −44, −46, −16) was situated anterior to the location typically reported for the VWFA. Greater activation for the controls was also observed in the right middle frontal gyrus.

FF vs. Fix: For false-fonts relative to baseline, typical readers exhibited greater activation relative to the dyslexics in the left superior parietal lobule, as well as in bilateral middle occipital regions.

RW vs. FF: The word-selective contrast yielded greater activation for controls relative to dyslexics in the left OTC, in the anterior portions of the VWFS (MNI: −38, −40, −20). This suggests less word-selective processing in this region in the dyslexics compared to their controls. Between-group differences were also observed in the left insula, the right lingual gyrus, and the right superior temporal gyrus.
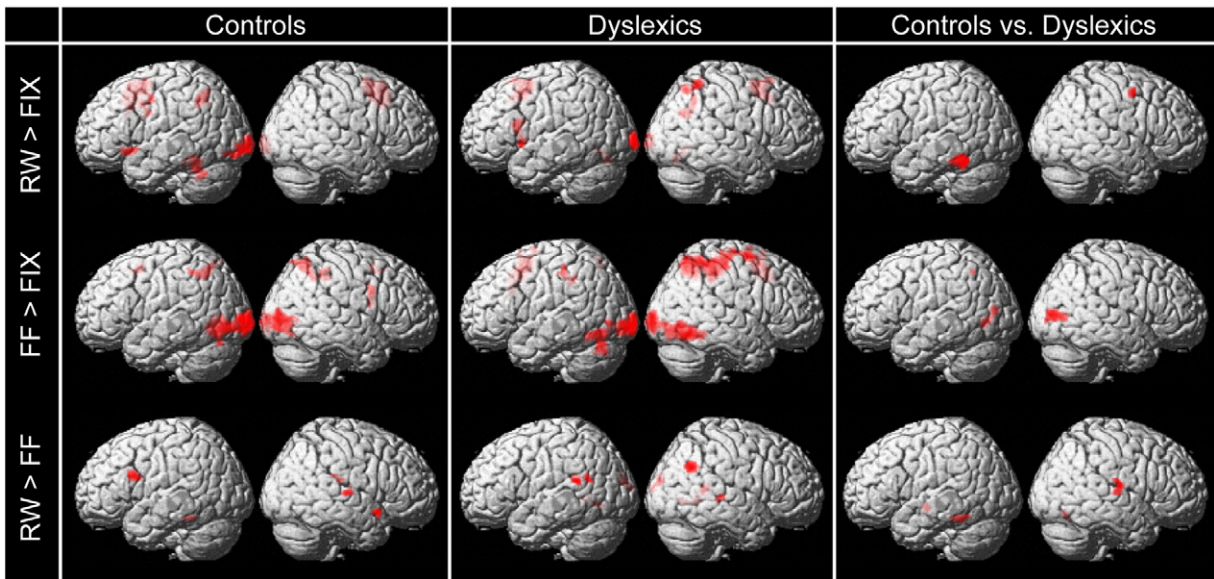
Fig. 1. Whole-brain activation maps surface rendered on the standardized MNI SPM brain template. Within-group maps are displayed for the control group and the dyslexic groups: *RW* > *Fix* (top) and *FF* > *Fix* (middle) maps were thresholded at $p < 0.001$ corrected for cluster size. *RW* > *FF* (bottom) maps were thresholded at $p < 0.001$ (uncorrected; minimum $k = 20$). *RW*: real words; *FF*: false-fonts. Between-group comparisons are shown for controls > dyslexics ($p < 0.001$, uncorrected for all conditions; minimum $k = 20$).

3.3. Gradient images in occipito-temporal and inferior frontal regions

3.3.1. Occipito-temporal regions

For typical readers we observed the expected pattern of differential activation in the left OTC. Greater activation for false-fonts (blue) was exhibited in posterior regions, with real word activity (red) being greater in more anterior regions (Fig. 2(A)). Visual inspection of these images did not reveal evidence of a gradient pattern along either the transversal (i.e. medial-to-lateral) or dorsoventral (inferior-to-superior) axes. As expected this pattern did not replicate in the right hemisphere.

When performing the same visualization in the dyslexic group, however, we did not find a gradient pattern of increasing word selectivity in the left or right hemispheres.

3.3.2. Inferior frontal regions

Using a similar visualization approach, this time in the IFC, the typically reading children demonstrated a gradient of increasing word selectivity. Specifically, increasing selectivity for words occurred along the transverse axis from the medial to lateral IFC, similar to the pattern previously reported in typically reading adults (Vinckier et al., 2007). As observed in Fig. 2(B), greater signal change occurred in response to false-fonts (blue) in medial left hemisphere inferior frontal regions, whereas real words (red) elicited greater activity in lateral regions. Similar to the VWFS, visual inspection of these images did not reveal evidence of a gradient pattern along either the anteroposterior or dorsoventral axes. No such pattern was observed in the right hemisphere for this group, again indicating specificity to the left hemisphere.

When the same procedure was repeated in the children with dyslexia, there was no evidence of a gradient of word selectivity in the left hemisphere (nor the right hemisphere).

3.4. Regions of interest

3.4.1. Occipito-temporal ROIs

We then used a region-of-interest analysis to statistically test the above described word selectivity patterns in OTC and IFC. Fig. 3(A) illustrates the locations of the ROIs in the left OTC. Contralateral, homotopic ROIs were also placed in the right hemisphere as a control. MNI coordinates of the ROIs were: *ROI* **1**: $[\pm42, -84, -10]$; *ROI* **2**: $[\pm46, -76, -12]$; *ROI* **3**: $[\pm46, -68, -14]$; *ROI* **4**: $[\pm42, -60, -14]$; *ROI* **5**: $[\pm46, -52, -18]$; and *ROI* **6**: $[\pm39, -44, -24]$. Mean percent signal change for *RW*−*FF* was calculated for all individuals in both groups within each of these regions (Fig. 3(A) — top right) and submitted to separate ANOVAs for each hemisphere.

In the typical readers, the left OTC region showed a pattern indicative of an increasing posterior-to-anterior selectivity for real words in the VWFS. Notably, a significant main effect of *ROI* was observed for this group ($F(5,7) = 2.61$; $P = 0.033$), and the analysis of linear trend was also significant ($F(5,7) = 11.229$; $P = 0.0001$; line slope = 0.11). This difference was driven by greater activity in response to real words than to false-fonts in the second most anterior region (t, $p =$ *ROI* 5: 3.62, 0.004). As anticipated, in the right hemisphere, there was no observed pattern of increasing activity from the posterior to the anterior regions via one-way ANOVA or via linear trend analysis ($F(5,7) = 1.06$ and 3.59 respectively; both $P > 0.05$).

However, when the same procedure was implemented in the dyslexic group, no significant main effect of *ROI* was observed ($F(5,11) = 0.62$; $P = 0.687$) and no linear trend was found ($F(5,11) = 0.79$, $P = 0.377$; line slope = 0.007) in the left hemisphere. There were also no findings in the right hemisphere homologues (ANOVA: $F(5,11) = 0.7$; linear trend: $F(5,11) = 0.01$; both $P > 0.05$).

When these were tested via a direct between-group comparison, the ANOVA (*ROI* × *Group*) yielded a significant main effect of *Group* ($F(5,23) = 16.02$; $P = 0.0001$) as well as a main effect of *ROI* ($F(1,27) = 2.99$; $P = 0.013$). Word-selective activity in this region was greater for the control group than for the dyslexics, and overall activity increased from the posterior to the anterior regions. There was a marginally significant interaction of *ROI* × *Group* ($F(5,23) = 1.94$; $P = 0.091$), suggesting that differences between the two groups in the nature of word-selective processing were dependent upon the location along the posterior–anterior axis of the OTC. Post-hoc *t*-tests revealed that *RW*−*FF* activity did not differ between the two groups in the posterior ROIs, but was significantly greater for the control group than the dyslexic group in the two most anterior regions (t, $p =$ *ROI* 5: 4.20, 0.0001; *ROI* 6: 3.06, 0.005). Turning to the right hemisphere control analysis, the ANOVA did not reveal any difference in activity between groups (main effect of *Group*: ($F(1,27) = 0.06$; $P = 0.805$)), no effect of *ROI* ($F(5,23) = 1.43$; $P = 0.214$), and no interaction of *ROI* × *Group* ($F(5,23) = 0.53$; $P = 0.754$).

Table 3
MNI coordinates and anatomical locations of whole-brain activation maxima.

Task	Group	MNI Co-ordinates x	y	z	Anatomical region	BA	k	Z	Group	MNI Co-ordinates x	y	z	Anatomical region	BA	k	Z
Real words > fixation	Controls	−16	−102	−8	L. cuneus	18	493	5.17	Dyslexics	−22	−102	4	L. middle occipital gyrus	18	238	5.22
		−38	−50	−24	L. fusiform gyrus	37	281	4.37		−2	−74	−16	L. cerebellum		170	4.27
		−26	−54	42	L. inferior parietal lobule	7	205	4.13		−50	10	−2	L. insula	13	253	4.72
		−38	−4	42	L. precentral gyrus	6	107	4.02		−4	12	48	L. medial frontal gyrus	6	656	5.20
		−52	14	−8	L. inferior frontal gyrus	47	95	4.08		32	−66	54	R. superior parietal lobule	7	175	3.97
		−2	8	4	L. superior frontal gyrus	6	1162	5.24		30	−58	42	R. angular gyrus	39	153	4.26
	Controls vs. dyslexics	−44	−46	−16	L. fusiform gyrus	37	297	4.76								
		36	−2	50	R. middle frontal gyrus	6	67	4.06								
False-fonts > fixation	Controls	−22	−98	6	L. middle occipital gyrus	18	1304	5.22	Dyslexics	−24	−102	0	L. middle occipital gyrus	18	1101	5.48
		−26	−58	46	L. superior parietal lobule	7	289	4.58		−46	−32	50	L. inferior parietal lobule	40	117	3.90
		−6	8	52	L. medial frontal gyrus	32	139	4.69		0	12	52	L/R. medial frontal gyrus	6	842	5.10
		18	−98	2	R. cuneus	18	584	4.57		48	−64	−14	R. inferior occipital gyrus	18	1133	5.55
		26	−62	56	R. superior parietal lobule	7	408	4.15		28	−64	56	R. superior parietal lobule	7	1442	5.21
		46	4	30	R. inferior frontal gyrus	9	109	4.13								
	Controls vs. dyslexics	−36	−72	0	L. middle occipital gyrus	39	105	4.46								
		−26	−58	48	L. superior parietal lobule	7	25	3.87								
		46	−84	8	R. middle occipital gyrus	19	200	3.93								
Real words > false-fonts	Controls	−40	−44	−18	L. fusiform gyrus	37	20	3.73	Dyslexics	−58	−56	20	L. superior temporal gyrus	22	23	3.66
		−50	12	24	L. inferior frontal gyrus	9	74	4.26		−14	−62	−4	L. lingual gyrus	19	28	3.56
										−6	−52	0	L. cerebellum		34	3.98
										−62	−44	18	L. superior temporal gyrus	22	43	3.58
		46	−32	24	R. inferior parietal lobule	13	24	3.89		8	−90	18	R. cuneus	18	54	3.78
		58	−22	6	R. superior temporal gyrus	41	40	3.68		8	−68	−2	R. lingual gyrus	19	32	3.95
		46	12	−14	R. superior temporal gyrus	38	45	4.61		54	−62	32	R. supramarginal gyrus	40	84	4.07
										10	−56	0	R. lingual gyrus	19	39	3.64
										28	−48	8	R. precuneus	7	60	3.68
										62	−30	4	R. superior temporal gyrus	22	21	3.59
	Controls vs. dyslexics	−38	−40	−20	L. fusiform gyrus	37	93	4.27								
		−32	−12	−10	L. insula	13	26	3.70								
		18	−70	−14	R. lingual gyrus	18	25	3.83								
		58	−18	8	R. superior temporal gyrus	43	100	3.98								

Together these results demonstrate, consistent with the gradient images above, selectivity for words in the anterior locations of the VWFS in skilled but not reading-impaired children. Using our data on standardized tests of reading performance, we illustrated this point in a different fashion by noting significant positive correlations between activity in ROI 6 and real word reading (WJ III WID, $r = 0.58$; $p = 0.001$) as well as pseudoword reading (WA, $r = 0.52$; $p = 0.005$; $n = 28$) when combining all subjects (dyslexic and typically reading children).

3.4.2. Inferior frontal ROIs

MNI coordinates of ROIs selected in the inferior frontal region were: **ROI 1**: [±20, 24, 10]; **ROI 2**: [±28, 20, 8]; **ROI 3**: [±38, 12, 4]; **ROI 4**: [±48, 12, −2]; and **ROI 5**: [±56, 12, −6]. Similar to the VWFS region, the control group exhibited a significant main effect of ROI ($F(4,8) = 6.60$; $P = 0.0002$) and a significant linear trend ($F(4,8) = 23.18$; $P < 0.0001$; line slope $= 0.09$), demonstrating an increase in selectivity for real words from the medial-to-lateral aspects of the IFC. This difference was driven by increasing activity for real words relative to false-fonts in the lateral regions (t, $p =$ ROI 4: 2.38, 0.036; ROI 5: 3.29, 0.007; Fig. 3(B), bottom). As expected, no consistent evidence for increasing word-selective activity was found in the homologous right hemisphere regions using similar analyses (ANOVA: $F(4,8) = 1.26$; $P = 0.298$; linear trend: $F(4,8) = 4.50$; $P = 0.04$; line slope $= 0.01$).
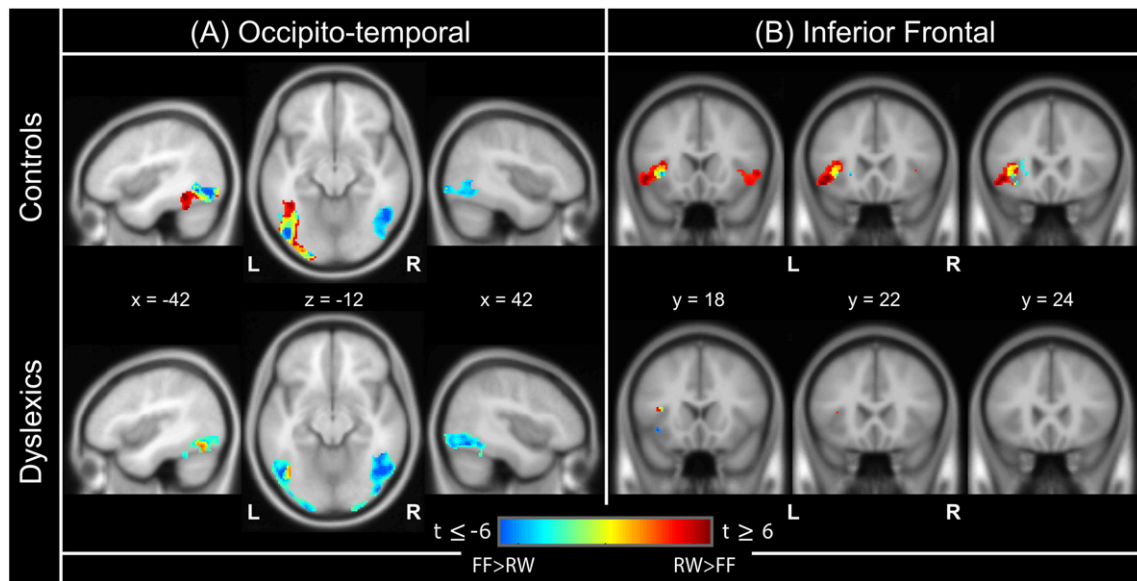
Fig. 2. Gradient images illustrating the layout of spatial sensitivity to real words (blue) and false-fonts (red) in occipito-temporal and inferior frontal regions. Differential activity (spmT maps) between real words and false-fonts was generated for each group using within-group whole-brain activation maps for each condition relative to fixation. fMRI *t*-statistic maps (*p* < 0.005; uncorrected) for *FF* vs. *Fix* were subtracted from the maps for *RW* vs. *Fix*. Resulting images were overlaid onto sectional slices using a standard MNI SPM brain template. These images are presented solely for the purpose of visualization of the gradients. (A) Maps illustrating differential activation between real words and false-fonts in the occipito-temporal cortex. Maps for the control group are shown at the top and for the dyslexic group at the bottom. (B) Gradient maps for control (top) and dyslexic (bottom) groups in the inferior frontal region. Images were masked to display activity contained within occipito-temporal and inferior frontal regions. *L*: Left hemisphere; *R*: right hemisphere; *RW*: real words; *FF*: false-fonts; *x*, *y*, and *z* coordinates represent locations in the standard MNI space. Color bar represents the gradient of sensitivity to each condition (*t*-statistic difference), with regions exhibiting greater activation for real words in red, and regions exhibiting greater activation for false-fonts in blue.

The dyslexic group exhibited comparable activation levels for both real words and false-fonts for all locations in the left hemisphere as well as the right hemisphere (ANOVA: $F(4,12)$ = left: 0.19, right: 0.27; both $P > 0.2$).

When comparing the two groups directly, the results from the two-way ANOVA of the left hemisphere confirmed a difference in pattern: there was a main effect of *Group* ($F(1,27)$ = 13.94; $P = 0.0003$), a main effect of *ROI* ($F(4,24)$ = 4.26, $P = 0.0028$), and a significant interaction of *ROI* × *Group* ($F(4,24)$ = 3.88; $P = 0.0052$). Post-hoc *t*-tests (Fig. 3(B)) revealed comparable activation levels between the two groups for the $RW - FF$ contrast in the medial portions of the IFC, while significant differences were observed between the groups in the most lateral region (t, p = ROI 5: 3.18, 0.004). Here, the control group exhibited greater activity than the dyslexic individuals. In the right hemisphere, there was no significant effect of *ROI* ($F(4,24)$ = 0.67; $P = 0.617$), but a significant effect of *Group* was observed ($F(1,27)$ = 7.52; $P = 0.007$), as the controls tended to have greater overall activity in this region compared to the dyslexics. Importantly, no interaction of *ROI* × *Group* was observed ($F(4,28)$ = 0.19; $P = 0.945$).

Together these results demonstrate a selectivity for words in the lateral location of the IFC in skilled but not reading-impaired children in ways that are similar to the profile described for the anterior OTC. Again, to establish brain–behavioral correlates, we examined the relationship of the fMRI data with standardized measures of reading and found in the full sample that activity in the most lateral *ROI* (*ROI* 5) was significantly correlated with WID ($r = 0.38$; $p = 0.048$) and WA ($r = 0.39$; $p = 0.039$; $n = 28$).

3.5. Connectivity analysis

In the typically reading children, there was evidence of connectivity during processing of real words based on a significant correlation for the regions in the anterior VWFS and lateral IFC (Fisher's $z = 0.61 \pm 0.95$; $p = 0.047$). However, there was no such correlation between the posterior VWFS and the medial IFC ($z = -0.10 \pm 1.29$; $p > 0.3$), that is, the regions not shown to be tuned to words. Turning to the dyslexic group, we

found no evidence for connectivity between either set of regions (anterior VWFS to lateral IFC: $z = 0.41 \pm 1.09$; posterior VWFS to medial IFC: $z = 0.29 \pm 1.76$ both $p > 0.2$).

4. Discussion

The goal of the current study was to test for the presence of hierarchical functional organization in the form of a gradient of increasing selectivity for real words in left hemisphere occipito-temporal and inferior frontal regions in English-speaking typically reading and dyslexic children. We used an implicit reading task that consisted of a real word reading condition and a false-font (non-lexical) visual control condition. Behaviorally, subjects performed with high accuracy on both conditions, and overall performance did not differ between the two groups. Using the more traditional whole-brain analysis, we first replicated the previously reported underactivity in dyslexics in the left OTC during real word compared to false-font processing (Pugh et al., 2001; Démonet et al., 2004; Maisog et al., 2008; Richlan et al., 2009; Hoeft et al., 2007). Next, for the purpose of visualization, we generated gradient images of differential activation between real words and false-fonts in the OTC and IFC. Then we statistically tested for region-specific within- and between-group differences in these areas using an ROI analysis technique. Similar to the study conducted in Swiss–German-speaking children (van der Mark et al., 2009), we observed a posterior-to-anterior gradient of increasing word selectivity in the left hemisphere OTC for the typically reading children, and absence of this in the dyslexic group. We then report for the first time on the existence of a medial-to-lateral gradient of increasing word selectivity in the left inferior frontal region for the typically reading children, similar to that which was previously reported in French-speaking adults (Vinckier et al., 2007). However, this pattern was absent in the dyslexic children, much in the way that it was absent in the dyslexics for the OTC. Finally, we tested for evidence of functional connectivity between regions in occipito-temporal and inferior frontal cortices based on selectivity for real words in both areas. We observed significant connectivity between word-selective areas of the OTC and IFC in the typically reading children,

but not the dyslexic children. Our results provide evidence of functional tuning for word-selective processing in inferior frontal and posterior left hemisphere brain regions in typically reading children, with an absence of these for children with reading disability.

4.1. Word selectivity in the occipito-temporal region

In our typically reading sample, the word-selective contrast (*RW* minus *FF*) conducted across the entire brain revealed an activation peak in the anterior portion of the VWFS. No activation was observed in this region for the dyslexic children, and a direct between-group comparison revealed significantly greater activation in the anterior VWFS for the typical readers relative to the dyslexic readers. These observations are consistent with previous reports citing hypoactivity in the OTC of dyslexic individuals for a variety of word processing tasks (Salmelin et al., 1996; Rumsey et al., 1997; Brunswick et al., 1999; Paulesu, 2001; Shaywitz et al., 2002; Cao et al., 2006; Maurer et al., 2007; Olulade et al., 2012) and with the meta-analysis results for both children and adults contrasting dyslexic with typical readers (Richlan et al., 2011). However, not all studies examining differences between dyslexics and controls have reported hypoactivity in this region (Schulz et al., 2008; Georgiewa et al., 2002; Georgiewa et al., 1999; Temple et al., 2001; Ingvar et al., 2002; Hoeft et al., 2006; Meyler et al., 2007), and these might be attributed to differences in the experimental paradigms employed as well as limitations in statistical power. The region-of-interest analysis technique employed in the current study is likely to reveal subtle differences that are not observed following more traditional whole-brain, voxel-wise analyses. Our results confirm a pattern of increasing word selectivity in the anterior VWFS regions for the typical readers, as previously reported for typical adult (Vinckier et al., 2007; Brem et al., 2006; Brem et al., 2009) and pediatric populations (Brem et al., 2009; van der Mark et al., 2009; Olulade et al., 2013) and its absence in dyslexia, as demonstrated in German-speaking children by van der Mark et al. (2009).

The relationship between reading ability and brain activity in the OTC can also be gauged in other ways: Our earlier study in typical readers demonstrated brain–behavioral relationships between the anterior occipito-temporal region and reading level (Olulade et al., 2013). Similarly, in the current study, single real word reading (WID from the WJ III Tests of Achievement (Woodcock et al., 2001)) correlated positively with percent signal change for real words greater than false-fonts in the left anterior occipito-temporal region. Together these findings add to a growing body of literature that demonstrates (a) a refined topography for word processing in the ventral OTC of successful readers, (b) an absence of this pattern in children with dyslexia, and (c) a direct relationship between brain activity measured here and reading ability assessed on standardized tests.

In our previous report (Olulade et al., 2013), we found developmental specialization of word processing to be present in more anterior occipito-temporal regions in adults compared to children. However, we also found that the gradient pattern of increasing selectivity for words was present (and thus established) in the pediatric typically reading sample, counter to the complete absence of any hierarchical organization shown here for the dyslexics. That is, the activation pattern in dyslexia does not represent a developmental delay, but rather a complete failure to establish a hierarchical pattern, either as a cause or a consequence of their reading problems. Theoretical models on the cause of dyslexia are mixed, and future studies are needed to weigh in on the exact pathway by which patterns of specialization in the occipito-temporal (and inferior frontal) regions fail to become established. The

absence of a gradient of increasing word selectivity for the English-speaking dyslexics in our study and for the Swiss–German-speaking dyslexics in the study of van der Mark et al. (2009) suggests that the manifestation of the disorder is independent of the orthographic depth of the language. How it differs depending on the orthography and whether such a pattern would be observed in dyslexic individuals in non-alphabetic languages such as Chinese is yet to be discovered.

4.2. Word selectivity in the inferior-frontal region

Studies on patients with acquired lesions in the left inferior frontal gyrus (Damasio, 1992; Rosen et al., 2000; Bizzi et al., 2012), as well as application of functional neuroimaging methods in healthy controls, have led to a greater understanding of the functional role of the left inferior frontal cortex. To date, it has been generally accepted that the dorsal portion of the IFC is involved in phonological processing (Pugh et al., 2001; Rumsey et al., 1997; Démonet et al., 1992; Fiez and Petersen, 1998; Poldrack et al., 1999; Owen et al., 2004), while the ventral portion subserves semantic aspects of word processing in typical readers (Thompson-Schill et al., 1997; Wagner et al., 2001; Badre et al., 2005; Whitney et al., 2011). Underactivation in this region has been reported for dyslexic children relative to their typically reading counterparts (Cao et al., 2006; Brambati et al., 2006; Booth et al., 2007; Schulz et al., 2008), and greater activation has been reported in some adult dyslexics (Brunswick et al., 1999; Shaywitz et al., 1998; Georgiewa et al., 2002). This has led to the idea of compensatory mechanisms in adults. However, there are also studies showing underactivation in dyslexic adults in the IFG, making it difficult to provide a unifying account of the findings to date. In fact, the meta-analyses conducted by Richlan and colleagues revealed underactivity here in adults with dyslexia, but not in children. As pointed out above, these brain imaging studies have primarily examined functional activity in this region in the context of performing whole-brain analyses, and more subtle differences may not emerge with this approach. Indeed, though our own whole-brain analysis revealed an activation peak in the lateral IFC for the word-selective contrast (*RW* minus *FF*) in the typically reading children, the between-group analysis did not reveal a difference in the children with dyslexia, consistent with the meta-analysis (Richlan et al., 2011).

When using the approach advanced by Vinckier et al. (2007) to determine if there exists a medial-to-lateral gradient in normally reading children in the IFC, we discovered varying response amplitude to words in the controls, similar to that previously described in normally reading adults, in the medial-to-lateral direction. Interestingly, this pattern was absent in the dyslexics, even though no difference was observed between the dyslexic and normally reading children at the whole-brain level of analysis. This may explain the variability in whole-brain investigations of dyslexia described above (e.g. with dyslexics being less versus equally active to controls in different reports). It also suggests the manifestation of a subtle difference in the IFC during childhood dyslexia that then becomes more obvious by adulthood. This characterization, which sets it apart from the OTC, could provide some interesting clues to the developmental trajectory of dyslexia and its etiology. One possibility is that the function of the IFC in dyslexia deteriorates with age.

In the context of reading measures, we found that when both groups were combined, we again observed a significant correlation between single real word and pseudoword reading (WJ III WID and WA) and condition-related activity (*RW* minus *FF*) in the lateral portion of the IFC. Thus, similar to the patterns observed in the VWFS, functional

Fig. 3. Region-of-interest analysis in left hemisphere occipito-temporal and inferior frontal regions. (A) Top left: ROIs in the left occipito-temporal region. *ROI* 1 represents the most posterior location, while *ROI* 6 is the most anterior location. *ROI* 5 (green) represents the location closest to the reported peak of the VWFA. (B) ROIs selected in the left inferior frontal region. *ROI* 1 represents the most medial location, while *ROI* 5 represents the most lateral location. (A & B) Top right: Mean percent signal change for real words minus false-fonts in the ROIs for the control (pink) and dyslexic (yellow) groups. Bottom: Mean percent signal change in each group for real words (red) and false-fonts (blue) separately. Error bars represent 1 S.E.M. *L*: Left hemisphere; R: right hemisphere.

(A) Occipitotemporal
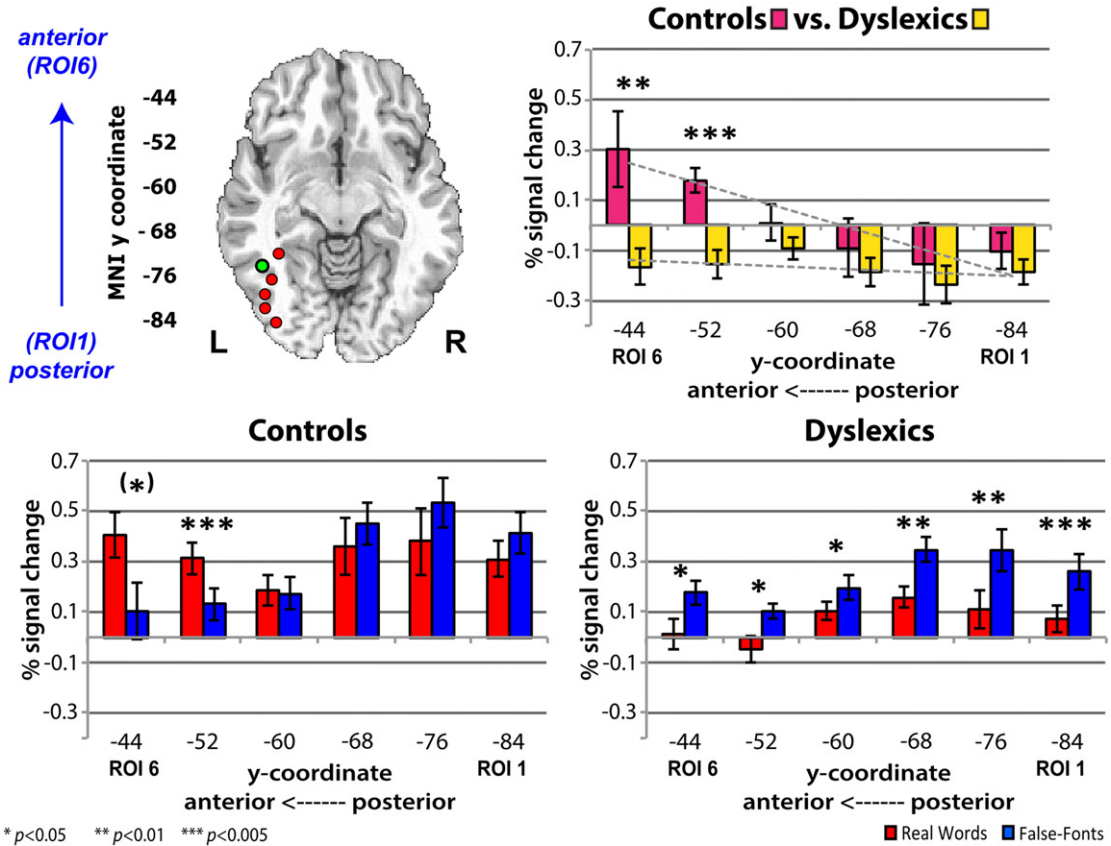
(B) Inferior Frontal
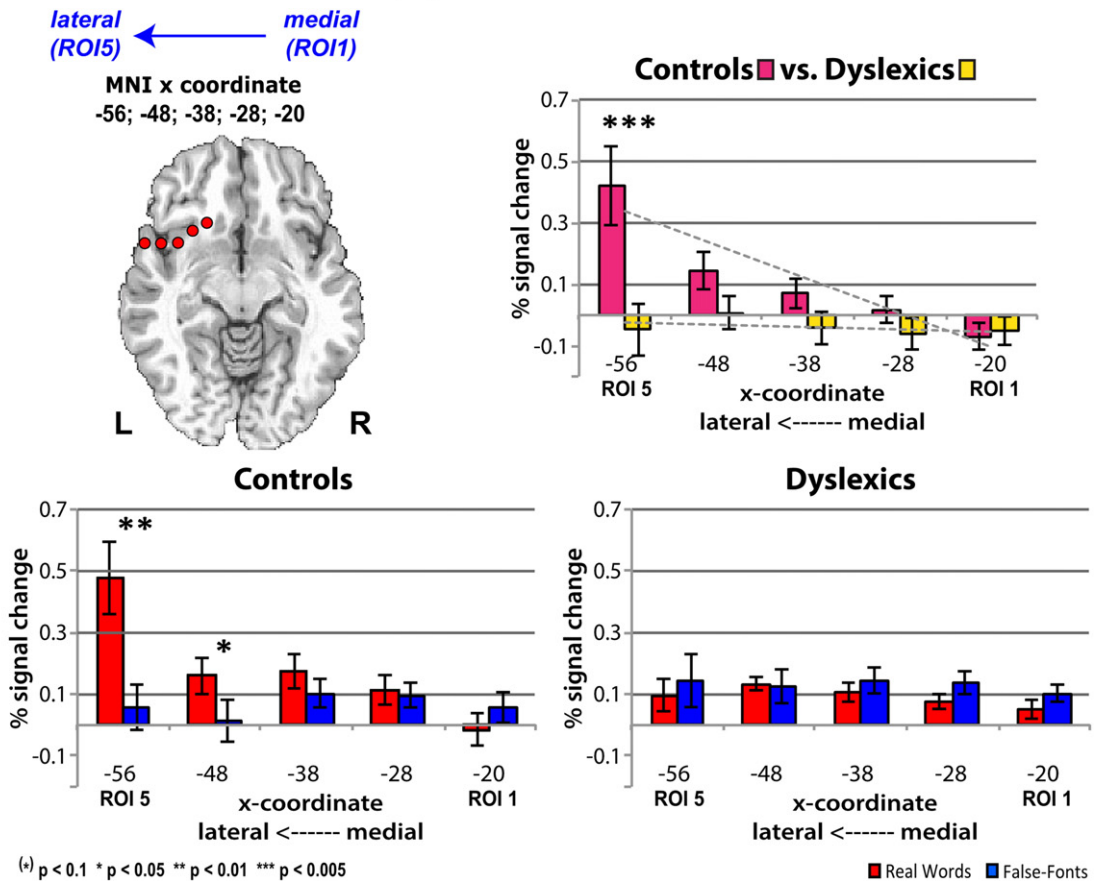
specialization occurs in the inferior frontal region in children who are strong readers, but not in impaired readers.

Given its more traditional role in phonological processing and articulation, it might seem surprising that the IFC shows gradients associated with neuronal tuning to words, similar to that found in the VWFS. Studies have, however, demonstrated wide-ranging responses here (particularly in the medial aspects), including a response to faces (Britton et al., 2006) and visual motion cues (Shulman et al., 1999). Importantly, recent models of reading propose a more direct role of the IFC in orthographic processing via grapheme-to-phoneme conversion (Richlan, 2014), as evidenced by greater reliance of this area during reading in languages with deeper orthographies such as English (Paulesu et al., 2000). Furthermore, the presence of functional connections between the IFC and OTC regions (Richlan, 2012; Richlan, 2014) suggests that some level of top-down modulation of OTC function by the IFC may be occurring. Of note is that according to this new model, in addition to orthographic whole-word processing, the OTC is proposed to also be involved in grapheme–phoneme conversion. Vinckier et al. (2007) postulated that neuronal connections between visual occipito-temporal areas and left hemisphere language regions might account for the duplication of the word-selectivity gradient pattern in both regions. Phonological remapping, as required for articulation, is subserved by the IFC (Pugh et al., 2001; Owen et al., 2004) and likely involves constant access to orthographic representations established within the OTC. Such continuous communication may lead to similar neuronal tuning in both of these left hemisphere regions.

We tested this hypothesis and found significant connectivity between *RW*-selective areas in the anterior VFWS and the lateral IFC in typically reading children. Other studies have provided evidence of other types of connections between occipito-temporal and inferior frontal regions. For example, a diffusion-weighted imaging study has revealed that the inferior fronto-occipito fasciculus contains fibers projecting from the occipital lobe through the OTC to the IFC (Yeatman et al., 2013). This anatomical study dovetails with physiological approaches that have demonstrated that these same connections might be modulated by specific task conditions. For example, Bitan and colleagues observed modulatory effects of rhyming and spelling on effective connectivity between inferior frontal and occipito-temporal fusiform regions (Bitan et al., 2005; Bitan et al., 2006). Reinke et al. (2008) described a "word-related network" via functional connectivity between the VWFA and left hemisphere middle frontal and hippocampal regions during word processing, but not during the processing of non-word stimuli (e.g. symbol strings and digits). Furthermore, Bokde et al. (2001) observed that functional connections between the left inferior frontal and occipito-temporal regions were modulated based on the location within the IFC, as well as the stimulus type. Specifically, functional connections between ventral (anterior) IFC (postulated to subserve semantic processing) and the occipito-temporal region were observed only during word processing, while connections between dorsal (posterior) IFC (postulated to subserve phonological processing) and the OTC were observed during processing of words, pseudowords, and consonant strings. These observations suggest that such connections between inferior frontal and occipito-temporal regions may topographically vary based on the functional specializations of the different locations within these regions. A subsequent study by Mechelli et al. (2005) further delineated the occipito-temporal fusiform region into anterior, middle, and posterior locations and used dynamic causal modeling to test the prediction that different locations in the IFC (i.e. anterior pars triangularis, middle-to-posterior pars opercularis, and posterior dorsal premotor cortex) that are sensitive to different word types (regular words, exception words, and pseudowords, respectively) would be functionally connected with different locations in the fusiform region based on sensitivity of these locations to the aforementioned word types. Their study found significant forward connections between the posterior fusiform region and the dorsal premotor cortex, and between the anterior fusiform region and the anterior pars

triangularis, again providing evidence of functional connections between the OTC and IFC that are modulated based on location and stimulus type. Importantly, van der Mark et al. (2011) demonstrated functional connectivity between the VWFA and a locus within the left hemisphere IFG in Swiss–German-speaking, typically reading children. This connectivity, however, was significantly weaker in their dyslexic group. Similarly, our own connectivity data did not reveal significant connectivity between the VWFS and IFC in the dyslexic children, further demonstrating the presence of altered connectivity patterns in dyslexia.

4.3. Lack of word selectivity in the inferior parietal region

Finally, given that studies of reading typically include the left inferior parietal cortex, the question arises whether a similar gradient might be observed here. Theoretically, it seems less likely, as the parietal cortex is usually assigned the function of phonological assembly (Pugh et al., 2001), and differences observed between dyslexic and typical readers in parietal cortex are typically explained on the basis of the phonological deficit that is associated with dyslexia. However, since parietal cortex is also intimately linked with the IFC anatomically (Kucyi et al., 2012), as well as in their function for phonological processing, the possibility of a reproduction of the patterns observed in the IFC does not seem impossible. Indeed, a connectionist view of reading would support the argument that the reading system is fully engaged during various aspects of word processing (Plaut et al., 1996), suggesting the presence of connections between the regions in this system. Vinckier and colleagues did not observe any pattern of specificity in the parietal region when examining whole-brain gradient images in adult typical readers (Vinckier et al., 2007), and similar inspection of gradient images in our current pediatric study did not reveal such patterns in the parietal region. Thus, it seems that the pattern of gradient selectivity is present only in the left inferior frontal and occipito-temporal regions in typical readers. This begs the question whether these two areas should be considered to have some shared properties, even though the traditional view is that the left inferior parietal and inferior frontal cortices make up the dorsal stream and are involved in assembled phonology, while ventrally located OTC handles addressed phonology, the more direct and fast pathway to reading frequently encountered words (Pugh et al., 2001). As pointed out by Richlan (2012), logographic reading (e.g. Chinese, which requires whole-word phonology) makes more use of OTC and IFC compared with alphabetic writing systems, which invoke activity in parieto-temporal cortices. Future studies in other languages and writing systems will be able to shed more light onto this question and further probe the role of the IFC in sublexical as well as lexical processing of words in typical and dyslexic readers.

5. Conclusions

In summary, our study reveals gradients of increasing selectivity for words in the OTC and IFC in typically reading children and functional connectivity between these regions. These gradients (and any functional connections) were absent in children with dyslexia. Our study provides information about models of dyslexia, particularly with respect to dysfunction of the IFC, and also adds to a growing body of literature suggesting a role of orthographic processing in this region.

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