Neural Responses of the Anterior Ventral Occipitotemporal Cortex in Developmental Dyslexia: Beyond the Visual Word Form Area

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Purpose. For the past 2 decades, neuroimaging studies in dyslexia have pointed toward a hypoactivation of the ventral occipitotemporal cortex (VOTC), a region that has been closely associated to reading through the extraction of a representation of words which is invariant to position, size, font or case. However, most of the studies are confined to the visual word form area (VWFA), while recent studies have demonstrated a posterior-to-anterior gradient of print specificity along the VOTC. In our study, the whole VOTC, partitioned into three main patches of cortex, is assessed in dyslexic and control adults.

Methods. A total of 30 participants were included in this study (14 developmental dyslexics and 16 age- and education-matched controls). The design consisted of alternately viewed blocks of stimuli from a given class (words, consonant strings, phase-scrambled words, phase-scrambled consonant strings, small checkerboards, large checkerboards). The analyzed contrast was print stimuli (words and consonants) versus scrambled stimuli and checkerboards.

Results. Corroborating previous findings, our results showed underactivation to print stimuli in the VWFA of dyslexics. Additionally, differences between dyslexics and controls were also found, particularly in an area of the anterior partition of the VOTC, suggesting a relevant role of this area in word processing.

Conclusions. In sum, our study goes beyond the underactivation hypothesis in the VWFA of dyslexics and indicates that a particular area on the anterior fusiform region might be particularly involved in the reading deficits in dyslexia, demonstrating the involvement of multiple areas within VOTC in reading processes.

Keywords: developmental dyslexia, fMRI, visual word form area (VWFA), ventral occipitotemporal cortex (VOTC)
Because activation in this region increases with reading skill, Shaywitz et al. referred to the left ventral occipitotemporal cortex (VOTC) as a “reading skill zone.” Since reading skills are impaired in dyslexia, it would be expected to find an underactivation of this region in this condition. In fact, this diversity was a concern already expressed by these authors, by highlighting an overview of 20 healthy brain. Although some authors have suggested that the dysfunctional activation of the VOTC is secondary to a primary dysfunction of the temporo-occipital reading system, the relevance of this region is highlighted in a study by Richlan et al., which reports the VOTC as the only area underactivated in dyslexics compared with nondyslexics in meta-analyses conducted in children as well as in adults.

Despite recent reports confirming that visual tuning follows a posterior-to-anterior gradient of increasing print specificity in the left occipitotemporal network in adults and adolescents as well as in children, most VOTC studies restrict themselves to the analysis of the VWFA, even when coordinates deviate from the ones defined by the early work by Cohen et al., who advert that this area is accurately found near Talairach coordinates −43, −54, −12, with a standard deviation of only ~0.5 cm in the healthy brain. In fact, this diversity was a concern already expressed by these authors, by highlighting an overview of 20 imaging studies reporting activations that fell within the following boundary coordinates: −50 < x < −30; −80 < y < −30; z < 0. The authors made a distinction between more anterior peaks, typically elicited by nonvisual verbal stimuli (or common to the visual and nonvisual stimuli), and the more posterior ones, consistent with their VWFA, observed when contrasting alphabetic strings with nonalphabetic stimuli such as false fonts or consonant strings. Implicit processing by passive viewing was chosen to avoid confounds driven by potential differences in task performance. Though the participants are not instructed to read the word during this task, reading occurs implicitly and without conscious effort in skilled readers. Various studies involving children and adults have demonstrated implicit processing activation in reading-related brain regions, including those thought to be involved in orthographic, phonologic, and semantic processing.

Word stimuli consisted of 60 five-letter words selected from the Portuguese Corlex database. Words with frequency values above 100 are considered to be highly frequent with the mean word frequency values for our sample being 1758.5. Consonant strings were built by combining 60 random series of five consonants (example: ‘cbtxt’). All of the consonant strings were unpronounceable in Portuguese.

Phase-scrambled versions were built for every word and consonant stimuli, in a total of 120.

Finally, two versions of checkerboards were built. A small version spanned the exact size of the word and consonant stimuli. A larger version had a threefold increase in the horizontal dimension and a 4-fold increase in the vertical dimension. This span was originally designed for use in a separate noise interference study on dyslexic subjects (data not shown) but was nonetheless used in this study to equate the number of acquired volumes per condition. The horizontal spatial frequency of the checkerboard stimuli was equated to the word and consonant stimuli (one black and one white square for each letter).

Materials and Methods

Participants

We recruited 14 developmental dyslexics (mean age: 30.50 ± 8.73, mean educational level: 15.64 ± 1.86) and 16 age-matched controls (mean age: 29.44 ± 6.72, mean educational level: 16.38 ± 2.03). The inclusion criterion for the dyslexics group was a previous clinical diagnosis of developmental dyslexia and no prior history of other developmental disorders. In the control group we included adults with no history of learning, developmental, cognitive, neurologic, or neuropsychiatric disorders.

All participants were assessed in terms of reading performance and intelligence level. For the reading assessment, a subtest from the Psycholinguist Assessments of Language Processing in Aphasia - Portuguese version (PALPA-P) was used. In this subtest, participants were asked to read a list of 60 words and pseudowords as quickly as possible. The measures obtained from this subtest were reading speed (in seconds) and accuracy (number of words correctly read). Intelligence level was measured through the Raven Progressive Matrices Test - Set 1 (RPM).

The groups were matched for age, sex, years of education, and IQ (as assessed by RPM), and statistically different in the reading measures (speed and accuracy). All participants were right-handed and had normal or corrected to normal vision.

Task and Stimuli

During fMRI acquisition, participants were asked to pay attention to presented words, consonants strings, checkerboards, and phase-scrambled versions of the words and consonant strings. The groups were matched for age, sex, years of education, and IQ (as assessed by RPM), and statistically different in the reading measures (speed and accuracy). All participants were right-handed and had normal or corrected to normal vision. Participants’ demographics and reading and intelligence scores are summarized in Table 1. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. Written informed consent was obtained from the participants, after an explanation of the nature and possible consequences of the study.

MR Scanning

Images were obtained on a scanner (Tim Trio 3T; Siemens Medical Solutions USA, Inc., Malvern, PA, USA) using a 12-channel head coil. Structural images were collected using a T1-weighted magnetization prepared rapid-acquisition gradient echo (TR = 2550 ms, TE = 3.42 ms, flip angle = 7°, matrix size = 256 × 256, voxel size = 1 mm³ isotropic). Standard T2-weighted gradient-echo echo planar imaging was used for the functional task runs (TR = 1500 ms; TE = 30 ms; 3.6 × 3.6 mm in-plane resolution; 3.6-mm slice thickness with no gap; flip angle = 76°; matrix size = 64 × 64; number of slices = 28; 285 measurements were used for the functional run). The slices were oriented to obtain a brain coverage spanning from the cerebellum to the motor cortices, ensuring ventral occipito-temporal coverage. Image processing was performed using commercial software (BrainVoyager QX v2.6; Brain Innovation, Maastricht, The Netherlands). Preprocessing steps included motion correction, slice scan-time correction, linear trend removal and temporal high-pass filtering of 0.00980 Hz (5 cycles in time course). Functional data were registered to each individual T1-weighted image using a nonlinear registration procedure.
individual’s anatomical scan and transformed to a common Talairach space.

The functional scan consisted of alternately viewed blocks of stimuli from a given class (words, consonant strings, phase-scrambled words, phase-scrambled consonant strings, small checkerboards, large checkerboards). The run had 18 blocks (three for each category) and each block lasted 20 seconds (20 images, 800 ms each, 200 ms gap), separated by 10-second fixation baseline intervals. The run started with a period of fixation for 10 seconds and ended with a period of fixation for 30 seconds. Block presentation order was pseudorandomized within each repetition (there had to be a block of each stimulus category before a second block of a given category could be presented) and then the same order was used for all participants.

DATA ANALYSIS

GLMs and Contrasts

A general linear model (GLM) with six predictors, one for each stimulus category was built for each participant. We focused on a contrast similar to the one used by Cohen to identify the VWFA, although we also included scrambled versions of words and consonant strings. In this manner, contrast was PRINT STIMULI (WORDS and CONSONANTS) versus SCRAMBLED STIMULI and CHECKERBOARDS.

VOTC Partitions

Following the reasoning outlined in the introduction, we parceled the VOTC into three ROIs, which approximately encompass the VWF system (among other dedicated areas): an anterior portion centered on $x = -35; y = -40; z = -20$, a middle portion centered on $x = -43; y = -60; z = -15$, and a posterior portion centered on $x = -40; y = -85; z = -5$. The regions span 25 mm along the $x$ dimension; 20 mm along the $y$ dimension and 30 mm along the $z$ dimension. The posterior region was allowed a larger span along the $y$ dimension to include posterior occipital activations.

The employment of a 3-fold division of this region in word processing studies is not new and has been successfully used by other authors.49,50 Furthermore, individual data corroborates this approach, as exemplified in Figure 1 for both dyslexic and control subjects. An illustration of the ROIs center and span is shown in Figure 2.

<table>
<thead>
<tr>
<th>TABLE 1. Summary Statistics for the Two Groups of Participants</th>
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<tbody>
<tr>
<td>Demographics and Clinical Variables</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Education, y</td>
</tr>
<tr>
<td>RPM</td>
</tr>
<tr>
<td>PALPA-P reading speed, s</td>
</tr>
<tr>
<td>PALPA-P accuracy</td>
</tr>
<tr>
<td>Sex, M/F</td>
</tr>
</tbody>
</table>

Probability values for group comparisons using t-tests (except for sex, for which the Chi square test was used) are reported ($P < 0.05$ values are considered significant).

FIGURE 1. Example of individual activations to the contrast words and consonants versus scrambled stimuli and checkerboards. Four controls (top row) and four dyslexics (bottom row) are shown. Note the pattern of the three identifiable clusters.
Anterior VOTC in Dyslexia

In his seminal VWFA study, Cohen and colleagues reviewed word-tuned activations that ranged from \( y = -80 \) to \( y = -30 \). In 2007, Vinckier et al. exploited the full range of this extension to argue in favor of a hierarchical coding of letter streams in the VOTC, from \( y = -96 \) to \( y = -40 \). They established that activation became more selective for higher-level stimuli toward the anterior fusiform region. Further research confirmed both the diversity and the posterior to anterior (ranging from low-level to high-level) direction of the word-tuned gradient. With this in mind, in the present study, we probed print-specificity in the whole VOTC, partitioned into three regions: anterior, middle, and posterior.

Corroborating previous studies, we demonstrated that dyslexics show hypoactivation to print stimuli in the VWFA (Talairach coordinates \(-43, -53, -6\)). Interestingly, we identified other areas in which print-specific activity is significantly larger for controls than dyslexics, particularly in the anterior partition of the VOTC, a region which sits at the top of the VOTC visual gradient and may bridge with nearby semantic and multimodal regions (for reviews, see Refs. 54 and 55). In fact, most robust differences were observed in an area of the anterior fusiform region (Talairach coordinates \(-51, -35, -18\)), which cluster size resulting from the statistical analysis suggests that this may be a distinct and relevant reading related area that would be worth investigating in future studies.

Other studies had located the brain region showing greater selectivity for letter strings in more anterior VOTC regions, rather than in the VWFA. Our study indicates that, adding to the VWFA, a specific area in the anterior VOTC might be particularly involved in the reading deficits in dyslexia, thus demonstrating the involvement of multiple areas within VOTC in reading processes.

According to the hierarchical coding of letter streams in the VOTC, bilateral early visual cortices extract the early features of the letters which are then recombined into increasingly abstract letter string representations up to the VWFA. The areas identified in the present study would therefore lie toward greater integration of print units, being responsible for whole word processing (VWFA) and even multimodal/semantic representation of words (anterior temporal cortex). Applying this framework to reading error analysis, disrupted neural activity at lower levels would predict errors on similar words (e.g., misreading “farm” as “form”), whereas noise at higher levels could lead to errors on increasingly larger units such that eventually the whole word is difficult to access. In this manner, the dyslexic pattern of activation in our sample would be more associated with difficulties at the whole-word higher perceptual levels whereas lower-level perception seems to be more preserved.

Nevertheless, the functional posterior-to-anterior hierarchy in the left VOTC has recently been challenged. In a very recent work, Lochy and colleagues report an extensive functional mapping of the VOTC for selective responses to visual letter strings and words with intracerebral recordings. Besides showing letter-selective responses across all the VOTC, they found responses to real words in a region extending more anteriorly than the VWFA. Moreover, a distinct spatial

**RESULTS**

For every VOTC partition, areas could be identified with greater activation for controls than dyslexics which are in concordance with coordinates previously reported in literature for word-processing relevant areas (see Table 2).

The significance map for the anterior partition is clearly dominated by an area in the left anterior fusiform gyrus, centered on Talairach coordinates \(-31, -35, and -18\). In the middle partition, an area with greater activity for controls than dyslexics was identified in close accordance to the reported coordinates of the VWFA \((-43, -53, -6\)). For the posterior partition, dyslexics showed significant hypoactivation for print stimuli in an area in the left posterior fusiform gyrus, centered on Talairach coordinates \(-34, -83, and -12\).

Thus, according to previous findings, we found underactivation to print stimuli in the VWFA of dyslexics. Nonetheless, the major differences between dyslexics and controls were found in the anterior partition of the VOTC, an intense debate has even been generated concerning its preservation in dyslexia. Previous work has identified hypoactivation of the VOTC in the dyslexic brain, particularly in the VWFA.

**DISCUSSION**

Since the early description of the VWFA in 2002, and the claim of a word tuning gradient in the VOTC, an intense debate has been generated concerning its preservation in dyslexia. Previous work has identified hypoactivation of the VOTC in the dyslexic brain, particularly in the VWFA.

**Table 2. Mean Contrast Differences in the Three VOTC Partitions**

<table>
<thead>
<tr>
<th>VOTC Partition</th>
<th>Controls &gt; Dyslexics</th>
<th>Controls</th>
<th>Dyslexics</th>
<th>t</th>
<th>p</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior partition</td>
<td>(−31; −35; −18)</td>
<td>0.845</td>
<td>−0.256</td>
<td>3.728</td>
<td>0.0008</td>
<td>786</td>
</tr>
<tr>
<td>Middle partition</td>
<td>(−43; −53; −6)</td>
<td>1.021</td>
<td>0.141</td>
<td>2.483</td>
<td>0.0193</td>
<td>48</td>
</tr>
<tr>
<td>Posterior partition</td>
<td>(−34; −83; −12)</td>
<td>1.354</td>
<td>−0.079</td>
<td>2.318</td>
<td>0.0280</td>
<td>7</td>
</tr>
</tbody>
</table>
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6. Stein J, Walsh V. To see but not to read; the magnocellular theory of dyslexia. *Trends Neurosci*. 1997;20:147–152.


