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Children with Dyslexia lack Multiple Specializations along the Visual Word-Form (VWF) System

Running Title:

Impaired Visual Word-Form System in Dyslexia

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Abstract

Developmental dyslexia has been associated with a dysfunction of a brain region in the left inferior occipitotemporal cortex, called the 'visual word-form area' (VWFA). In adult normal readers, the VWFA is specialized for print processing and sensitive to the orthographic familiarity of letter strings. However, it is still unclear whether these two levels of occipitotemporal specialization are affected in developmental dyslexia. Specifically, we investigated whether (a) these two levels of specialization are impaired in dyslexic children with only a few years of reading experience and (b) whether this impairment is confined to the left inferior occipitotemporal VWFA, or extends to adjacent regions of the 'VWF-system' with its posterior-anterior gradient of print specialization. Using fMRI, we measured brain activity in 18 dyslexic and 24 age-matched control children (age 9.7-12.5 years) while they indicated if visual stimuli (real words, pseudohomophones, pseudowords and false-fonts) sounded like a real word. Five adjacent regions of interest (ROIs) in the bilateral occipitotemporal cortex covered the full anterior-posterior extent of the VWF-system. We found that control and dyslexic children activated the same main areas within the reading network. However, a gradient of print specificity (higher anterior activity to letter strings but higher posterior activity to false-fonts) as well as a constant sensitivity to orthographic familiarity (higher activity for unfamiliar than familiar word-forms) along the VWF-system could only be detected in controls. In conclusion, analyzing responses and specialization profiles along the left VWF-system reveals that children with dyslexia show impaired specialization for both print and orthography.

Introduction

Developmental dyslexia is a severe, specific disorder of reading acquisition with a high prevalence and familial risk (Schulte-Körne, 2001). Converging evidence from neuroimaging studies investigating dyslexia suggests functional deficits in brain regions involved in reading, including left inferior frontal gyrus, left parietotemporal cortex and left occipitotemporal gyrus (for a review see (Shaywitz and Shaywitz, 2005)). Next to the well-documented phonological core deficit in dyslexia (Ramus et al., 2003), another major deficit in individuals with dyslexia is the impaired automaticity of visual word processing, which prevents skilled, fluent (automatic) reading. While neuroimaging studies in normal-reading adults have identified a particular part of the left inferior occipitotemporal cortex, called the visual word-form area (VWFA, hereafter also referred to as “the VWFA proper”; Talairach coordinates: $\pm -43 -54 -12$, with a standard deviation of ± 5 mm) (Cohen et al., 2000), as being specialized for visual word processing, studies in dyslexic readers implicate a dysfunction in this left inferior occipitotemporal region (for a review see Shaywitz and Shaywitz, 2005). More specifically, in normal-reading adults at least two levels of VWFA specialization have been proposed to exist: a fast, coarse form of visual tuning for print (letter strings vs. visual control stimuli) and specialization at the whole-word level, i.e. more efficient processing of familiar than unfamiliar word-forms, also called orthographic familiarity effect (Bruno et al., 2008; Kronbichler et al., 2007). However, functional magnetic resonance imaging (fMRI) studies examining visual tuning for print in the VWFA of healthy adults provide inconsistent results. While some studies found that words evoke stronger activation in the VWFA than visual control stimuli such as checkerboards (Cohen et al., 2002), false-fonts (Vinckier et al., 2007), or pictures (Gauthier et al., 2000; Hasson et al., 2002), other studies found similar activation for both words and false-fonts (Brem et al., 2006; Brem et al., 2009;

Tagamets et al., 2000). The second level of VWFA specialization concerns orthographical familiarity with letter strings. In adults and adolescents, pseudohomophones (PH, phonologically familiar but orthographically unfamiliar forms of real words) and pseudowords (PW, phonologically and orthographically unfamiliar word-forms without semantic content) were shown to evoke stronger activation than real words in the VWFA (Bruno et al., 2008; Kronbichler et al., 2007).

Furthermore, previous studies in healthy subjects demonstrated that visual tuning to words is not confined to the VWFA. Rather, a posterior-to-anterior gradient of increasing print specificity was found in a left occipitotemporal network (VWF-system) in adults and adolescents (Brem et al., 2006; Brem et al., 2009; Vinckier et al., 2007) as well as in children (Brem et al., 2009). Similarly, effective connectivity with prefrontal activity during the reading of regular words, exception words, and pseudo-words showed selective increase with distinct occipitotemporal areas (posterior, middle, anterior fusiform), depending on word-type (Mechelli et al., 2005). A priming study of Dehaene et al. (2004) demonstrated that posterior but not anterior fusiform regions are sensitive to small changes in letter position, suggesting that binding of letters into words is accomplished by a posterior-to-anterior gradient of increasingly invariant processing of letters in the left occipitotemporal cortex (Dehaene et al., 2004). However, since most previous studies examining dyslexia focused on the VWFA proper, it remains to be determined whether dyslexia-related impairments in visual word-form processing are limited to the VWFA proper or whether such a dysfunction affects the occipitotemporal VWF-system and its gradients of specialization. Therefore, VWF-system gradients for both print and orthography were investigated in the present study.

Several studies on visual word processing in dyslexic readers implicate a dysfunction in the left inferior occipitotemporal cortex. Recently, it was demonstrated

that dyslexic adults and adolescents did not show the orthographic familiarity effect in the VWFA (Wimmer et al., personal communication) characterizing nonimpaired readers (Bruno et al., 2008; Kronbichler et al., 2007). Moreover, functional neuroimaging studies investigating dyslexia found the VWFA to be generally underactivated during word reading in adults and adolescents (Brunswick et al., 1999; Helenius et al., 1999; McCrory et al., 2005; Paulesu et al., 2001; Rumsey et al., 1997a; Rumsey et al., 1997b; Salmelin et al., 1996; Shaywitz et al., 2003; Wimmer et al., personal communication) as well as in children (Cao et al., 2006; Maurer et al., 2007; Shaywitz et al., 2002; Shaywitz et al., 2007). It is important to note that most of these previous studies found a *general* underactivation in the VWFA, rather than a *specific* impairment of the two levels of specialization (i.e. more efficient processing of one stimulus type versus another). Such a general underactivation was commonly identified by contrasting e.g. words or pseudowords with a low-level baseline consisting of crosshair fixation (Cao et al., 2006; Rumsey et al., 1997a; Rumsey et al., 1997b; Wimmer et al., personal communication), symbol strings (Helenius et al., 1999; Maurer et al., 2007), a line judgment task (Shaywitz et al., 2002; Shaywitz et al., 2003), or rest with eyes closed (Brunswick et al., 1999). So far, a single study reported reduced left occipitotemporal activation in dyslexics vs. controls for the comparison of words with a high-level baseline consisting of false-fonts (McCrory et al., 2005). Finally, no study so far has compared both levels of word processing in young normal-reading and dyslexic children in a systematic manner. Thus, it still remains to be seen whether dyslexia-related impairments in visual word-form processing affect the VWF-system and its gradients of specialization in dyslexic children with only a few years of reading experience.

The aim of this study was to test the hypothesis that a dysfunction of specialization within the VWF-system for processing both print and orthographic

familiarity is already present in young children with dyslexia. We used fMRI to examine the activation gradients along the left occipitotemporal cortex of control and dyslexic children. The participants performed a phonological lexical decision task (“Does it sound like a real word?”) including four types of letter strings varying in orthographic familiarity, i.e. real words (familiar word-forms; e.g., Taxi), pseudohomophones and pseudowords (unfamiliar word-forms; e.g., Taksi and Tazi, resp.), and false-fonts (visual control stimuli). We expected control children to show a dissociation of two *functional* levels of specialization within the VWF-system: (1) coarse specialization for print, i.e. differential processing of letter strings (real words, pseudohomophones and pseudowords) vs. visual control stimuli (false-fonts) and (2) sensitivity to orthographic familiarity, i.e. more efficient processing of familiar than unfamiliar visual word-forms. Furthermore, we expected children with dyslexia to show impairments on both of these functional levels of VWF-system specialization. Finally, we aimed to clarify whether a potential dysfunction in children with developmental dyslexia is *spatially* confined to specific regions or extends over the full range of the VWF-system along the posterior-anterior axis of the occipitotemporal gyrus.

Materials and Methods

Participants

The 42 children (mean age 11.3 yrs, ± 0.6 yrs) who participated in this study were grouped according to their reading scores (see Table 1): 18 children with dyslexia and 24 control children. Twenty-six children were part of an extensive longitudinal study investigating developmental dyslexia in children (Maurer et al., 2007; Maurer et

al., 2003; Schulz et al., 2008) and 16 children participated only in either 4th or 5th grade. Eight additional children were excluded from analysis: 1 child due to head movement exceeding the a-priori maximum movement criterion ($> \pm 2$ mm translation or $> \pm 2^\circ$ rotation), 7 children because of poor performance (accuracy $< 60\%$ in one or more conditions) in the phonological lexical decision task ($n = 5$) or in the orthographical task ($n = 2$).

The children were screened for a history of neurological diseases or psychiatric disorders and reported all normal or corrected-to-normal vision. Children from families with a foreign language background (i.e. both parents' first language was not (Swiss-) German) were excluded from the study. The children were contacted by distributing handouts at schools. The children and their parents/caretakers gave their informed written consent to participate in the study. The study was approved by the local ethical committee.

Subjects were submitted to a typical test battery for German dyslexia (Mayringer and Wimmer, 2000; Wimmer, 1996, 2006; Wimmer et al., 2000) using the correct word-per-minute reading score as a reading fluency measure, which is the core criterion for diagnosing dyslexia in readers of the regular German orthography (Wimmer et al., 2000). The children tested in the 4th grade ($n = 6$), were grouped based on their "correct words per minute" reading score of the Salzburg Reading and Spelling Test ("Salzburger Lese- und Rechtschreibtest" (SLRT) (Landerl et al., 1997)), a test designed to assess dyslexia in children in 2nd to 4th grade. Reading skills of the children tested in 5th grade ($n = 36$) were assessed with the "Ein-Minuten Leseflüssigkeitstest" (Landerl and Willburger, in press), which required the children to accurately read as many words as possible from a list within 1 minute. The "correct words per minute" score of the 4th graders was compared to the published SLRT norms (Landerl et al., 1997), the "correct words per minute" score of the 5th graders

was compared to the distribution in a normative group of 56 children, as detailed in (Schulz et al., 2008). All children from the present fMRI study were categorized as dyslexic if their “correct words per minute”-score was below the 10th percentile of the corresponding norms, and as control children if their score was equal to or above the 20th percentile of the norms. As can be seen in Table 1, the children with dyslexia performed worse not only on word reading (the criterion for grouping), but also on pseudoword reading.

Nonverbal and verbal intelligence was estimated using the block design and the similarities subtest of the HAWIK-III intelligence test (Tewes et al., 2000). The groups were matched for gender, age, and handedness. Furthermore, estimated verbal IQ did not differ between the groups and particularly non-verbal IQ was well-matched, as expected (Table 1). In addition, all parents filled out a questionnaire regarding the child’s handedness (Edinburgh Handedness Inventory (Oldfield, 1971)). Finally, spelling scores consist of the mean % correctly written words of pooled SLRT scores of the 4th graders and DRT-5 scores (Diagnostischer Rechtschreibtest (Grund et al., 1995)) of the 5th graders.

Please insert Table 1 approximately here

Stimuli and Task

During fMRI acquisition, participants performed a phonological lexical decision task in which they had to decide if a visually presented stimulus sounded like a real word or not (Kronbichler et al., 2007). The 176 stimuli consisted of 44 orthographically familiar forms of German nouns (W), 44 pseudohomophones (PH; phonologically correct but

orthographically unfamiliar forms of the same words), 44 pseudowords (PW; phonologically and orthographically unfamiliar forms) and 44 false-fonts (FF). Additionally, 65 null events (fixation cross only) were presented. The stimuli were presented in a pseudo-randomized fashion, and the order of the stimuli was the same for all participants.

The letter string stimuli (W, PH, PW) used were the same as in the study of Kronbichler et al. (Kronbichler et al., 2007) with minor adaptations because the children in our study speak a different German dialect (Swiss-German). However, an essential difference from the task of Kronbichler et al. is that we added false-font (FF) strings as non-lexical control stimuli. For each letter, upper and lower case, a FF character was created. In contrast to previous studies (Bruno et al., 2008; Kronbichler et al., 2007), there were just as many trials requiring a “yes” response as a “no” response, due to the inclusion of the FF items. This excluded the possibility of a response bias toward “yes” responses. The characteristics of the four item types are shown in detail in Table 2 and a complete listing of all stimuli used can be found in Supplementary Table 1 online. All stimuli were matched for complexity, character size, and number of characters in a string (3-6 characters; average horizontal visual angle: 2.2°, range: 1.3-3°). In addition, the letter string types were matched for bigram frequency.

In the event-related design, the stimuli were presented for 700 ms with an interstimulus interval (ISI) of 2550 ms during which a fixation cross was shown. Participants were instructed to press ‘Yes’ for W (e.g. Taxi) and PH (e.g. Taksi) and to press ‘No’ for PW (e.g. Tazi) and FF. For responding, they used the index finger and middle finger of their dominant hand. Yes- and No-Buttons were counterbalanced across participants and groups. Responses were made via a fibre-optics response button box (Lumina LP-400, Cedrus Corporation, San Pedro, USA)

and stimulus delivery and response registration was controlled by Presentation (Neurobehavioral Systems Inc., Albany, CA, USA). To become familiar with the task, the subjects were given a short practice version (with different stimuli) of the task outside the scanner. In addition to the fMRI session, the participants also performed the task during an ERP session, of which the results are not further discussed here. The order of the ERP and fMRI session was counterbalanced across subjects and groups.

A separate orthographic judgment task (i.e., “Is this a correctly spelled word?”), which included the W-, PH- and PW-items of the experimental task but no FF stimuli, determined the participants’ ability to differentiate the familiar (W) from the unfamiliar, misspelled, forms of the same words (PH). This task was self-paced and was performed immediately after MRI acquisition.

fMRI Acquisition

MRI data was acquired on a 3.0 T (GE Healthcare) whole-body scanner. For functional imaging, 535 functional images sensitive to BOLD contrast with 25 axial slices covering the whole brain were acquired with a T2*-sensitive multi-slice echo planar imaging (EPI) sequence (TR = 1.5s; TE = 31ms; FOV = 24cm; image matrix = 64 x 64; voxel size = 3.75 x 3.75 x 5 mm³; flip angle = 50°). The first 4 scans were discarded to allow for equilibration effects. Participants were fitted with earplugs and viewed the stimuli via TFT video goggles (Resonance Technology Inc., California, USA). Particular care was taken to stabilize the children by using vacuum cushions and custom made padding.

Region of Interest Analyses

Five non-overlapping regions of interest (ROIs; spheres with a 5mm radius) were defined, covering the putative VWFA of the fusiform gyrus (Cohen et al., 2000) and neighbouring areas along a posterior-anterior axes in the left hemisphere, following the slight anterior decline of the temporal lobe. The ROI coordinates were based on those of Brem et al. (2006): ROI1 (MNI coordinates (x/y/z): -42, -34, -20), ROI2 (-42, -44, -18), ROI3 (VWFA proper; -42, -54, -17), ROI4 (-42, -64, -16), and ROI5 (-42, -74, -14). The mean percent signal change values in these ROIs were computed using the MARSBAR toolbox in SPM5 (<http://marsbar.sourceforge.net/>) (Brett et al., 2002) on unsmoothed data.

Statistical Analyses

The behavioural data of both the experimental and the orthographic judgment task, response accuracy and reaction times (correct trials only) were analyzed separately in a repeated measures analysis of variance (ANOVA) with the within-subject factor 'condition' (W, PH, PW, FF) and between subject factor 'group' (dyslexics and controls) (Table 2). Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, USA).

Functional MRI data preprocessing and statistical analysis was done using SPM5 (Wellcome Department of Imaging Neuroscience, London, <http://www.fil.ion.ucl.ac.uk/spm>). The data were first motion corrected and the images were then normalized using a 4th Degree B-Spline interpolation method to match the Montreal Neurological Institute (MNI) EPI template. Finally, functional volumes were resampled to isotropic 3 mm³ voxels and spatially smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel.

Statistical analysis of the fMRI data was performed in a two stage mixed effects model. In the subject-specific first level model, the event-related activation

evoked by each trial type (W, PH, PW, FF) was modelled using the standard SPM hemodynamic response function with its temporal derivative. To control for performance-related confounds, only correct trials were used in the statistical analysis. Correct and incorrect responses were modelled separately in the design matrix and a covariate of no interest was entered. The data were temporally high-pass filtered with a frequency cut-off period of 128s, and serial correlations were accounted for using an autoregressive model of the first order. Condition and group analyses were conducted with second-level random-effect *t*-tests using the individual contrast images. Statistical parametric maps of *t* values were generated. One-sample *t*-tests across all participants in each group were performed to determine whether activation within a group was significant. Clusters ($k > 10$) including voxels exceeding a false discovery rate (FDR) corrected $P < .05$ were considered to show significant activations (Genovese et al., 2002). Paired *t*-tests were performed to determine whether there were reliable differences between conditions. Words were contrasted with false-fonts (W vs. FF) to investigate visual specialization for print vs. visual control stimuli. Furthermore, pseudohomophones were contrasted with words (PH vs. W) and pseudowords with words (PW vs. W), both reflecting the orthographic familiarity effect, i.e., more activity for orthographically unfamiliar than for familiar letter strings. In addition, two-sample *t*-tests (control vs. dyslexic children) were computed to determine whether there were reliable group differences. For paired and two-sample *t*-tests, a $P < .001$ uncorrected for multiple comparisons and a cluster size $k > 10$ were used to determine significantly activated areas. While our threshold of uncorrected $p < .001$ may seem liberal at first, it is in fact comparable to (Booth et al., 2007; Cao et al., 2006; Hoeft et al., 2007; Wimmer et al., personal communication) or better (Brambati et al., 2006; Kronbichler et al., 2006) than most of the previous fMRI papers reporting effects in the VWFA in dyslexia. Activated brain

structures were identified by transforming the MNI coordinate system into the standard brain atlas of Talairach and Tournoux (Talairach and Tournoux, 1988), using `mni2tal.m` (provided by Matthew Brett; <http://www.mrcmbu.cam.ac.uk/Imaging/Common/mnispace.shtml>).

For the ROI analysis of the fMRI data, a repeated measures ANOVA with the within-subject factors 'condition' (W, PH, PW, FF), 'ROI' (ROI 1, 2, 3, 4, 5), and between subject factor 'group' (dyslexics and controls) was computed. Next, separate ANOVAs were computed to contrast specific conditions, i.e., for W and FF, PW and FF, mean(W, PH, PW) and FF, PH and W, and finally PW and W. Although averaging the three letter string conditions for comparison to FF eliminates the different mean levels, this average accurately captures the difference in gradients (e.g., slopes or profiles over ROIs) between letter strings and FF. In an ANOVA including only the letter string conditions but excluding the false-fonts, the interaction of ROI*condition*group was no longer significant. The post-hoc tests used to follow up significant ANOVA effects are reported using the uncorrected $P < .05$ threshold; adjusting for multiple testing of the 5 ROIs would have required $P < .01$.

Results

Behavioural Results

Reaction time, accuracy and p -values of group comparisons for the phonological lexical decision task and the orthographical judgment task are reported in Table 2. In the phonological lexical decision task performed inside the scanner, accuracy scores differed significantly between conditions ($F(3,38) = 74.60, P < .001$) and groups

($F(1,40) = 13.68, P = .001$). In addition, an interaction of condition with group was found ($F(3,38) = 9.83, P < .001$). Post-hoc t -tests revealed that children with dyslexia made significantly more mistakes than control children for PH (more erroneous “no” responses) and for PW (more erroneous “yes” responses), whereas the groups performed equally well for W and FF.

Analysis of the reaction times yielded significant main effects of condition ($F(3,38) = 170.22, P < .001$) and group ($F(1,40) = 17.05, P < .001$) in addition to an interaction of condition with group ($F(3,38) = 21.09, P < .001$). Post-hoc t -tests revealed that the children with dyslexia responded more slowly than the control children to all three letter string conditions. Note that there was no significant group difference for FF.

Performance on the orthographic judgment task (i.e., “Is this a correctly spelled word?”) outside the scanner, revealed an accuracy difference between conditions ($F(2,39) = 38.42, P < .001$), and a highly significant condition by group interaction ($F(2,39) = 13.30, P < .001$). Post-hoc t -tests revealed that dyslexics made more mistakes than control participants for PH.

Please insert Table 2 approximately here

fMRI Results

Conditions Contrasted Against Fixation

Contrasts of each separate condition against fixation are shown in Figure 1. A detailed listing of the activation clusters is provided in Supplementary Table 2 online.

As expected, all three letter string conditions activated predominantly left hemispheric language regions (e.g. superior temporal, fusiform, superior parietal and inferior frontal gyrus) in both controls and dyslexic readers. False-fonts evoked mostly activation in bilateral occipital regions (fusiform gyrus, medial occipital gyrus and left inferior occipital gyrus) and left parietal areas (precentral and postcentral gyrus) in control children but no significant activation in the children with dyslexia at the current threshold. However, when the threshold was lowered to $P < .05$ uncorrected, similar regions were found to be active in the children with dyslexia and the control children.

Comparing the control vs. dyslexic children for W and FF vs. fixation revealed no significant group differences. For PH vs. fixation, control children showed more activation than the children with dyslexia in the bilateral middle frontal gyrus, inferior parietal lobule and insula as well as the left fusiform gyrus. For PW vs. fixation, controls showed more activation than dyslexics in left inferior parietal lobule.

Please insert Figure 1 approximately here

Next, Figure 2 and Table 3 show the results of the main contrasts for each group separately. A detailed listing of the results of the comparison of FF, PH and PW with the orthographically familiar W for each group separately as well as the comparison between groups is provided in Supplementary Table 2-4 online.

Comparison of Words with Visual Control Stimuli

The contrast W vs. FF in control readers revealed activation in bilateral inferior frontal gyrus, left medial and superior frontal gyrus as well as in the left insula. When the

threshold was lowered to $P < .005$ uncorrected, stronger activation for W than FF was also detected in left anterior fusiform gyrus (MNI coordinates: $x = -48$, $y = -45$, $z = -21$) in controls (Figure 4). The opposite contrast (FF vs. W) showed activation maxima in left posterior fusiform gyrus and left middle and right superior occipital gyrus. In children with dyslexia, W evoked stronger activation than FF in the bilateral inferior frontal and left middle and superior frontal gyrus and the right lingual gyrus, and FF evoked stronger activation than W in right inferior parietal lobule. Finally, control children showed stronger activation than dyslexic children in left inferior and middle occipital gyrus, bilateral posterior cingulate gyrus and the left hemispheric cuneus for the contrast FF vs. W. The group comparison for W vs. FF showed no significant voxels.

Comparison of Unfamiliar with Familiar Word-Forms

For the contrast PH vs. W, the controls demonstrated stronger activation for PH in left superior parietal lobule, left and right inferior frontal gyrus, the left precuneus, the left fusiform gyrus, the right insula, left medial and right superior frontal gyrus and right inferior and superior parietal lobule. No region showed higher activation for W than for PH. In the children with dyslexia, brain area showing stronger activation for PH than for W included bilateral inferior and medial frontal gyrus and superior parietal lobule. The cortical activations for the opposite contrast W vs. PH in dyslexic children included the left middle frontal gyrus, and the right hemispheric superior temporal, superior frontal gyrus, inferior parietal lobule, precuneus and angular gyrus. For the group comparison, we found that the contrast PH vs. W showed more activation in the control than the dyslexic children in the left inferior parietal, superior temporal gyrus, and the left insula. No differences between groups were found for the contrast W vs. PH.

The contrast of PW with W in controls yielded activations comparable to the contrast PH vs. W, with complementary activity in the left superior temporal and right middle frontal gyrus. The opposite contrast (W vs. PW) indicated activation in the left hemispheric superior and medial frontal gyrus, inferior parietal lobule, insula, bilateral cingulate gyrus and angular gyrus. In children with dyslexia, the contrast PW vs. W yielded slightly stronger activation than PH vs. W. Activated regions included the left hemispheric precentral gyrus, left middle occipital and inferior and superior frontal gyrus, superior parietal lobule and right hemispheric cingulate gyrus. The opposite contrast W vs. PW yielded activations similar to W vs. PH, with additional activity in the left hemispheric superior frontal and angular gyrus, the left precuneus as well as the right hemispheric inferior parietal lobule and bilateral cingulate gyrus. Finally, the contrasts PW vs. W and W vs. PW did not distinguish the groups.

Please insert Table 3 approximately here

Please insert Figure 2 approximately here

Visual Word-Form System

Brain responses were further investigated in five regions of interest in the left and right occipitotemporal cortex (Figure 3). Gradient images illustrating the spatial layout of the sensitivity of the occipitotemporal cortex are displayed in Figure 4. Since we were most interested in the effect of condition on left occipitotemporal activation in

each group of children, we will focus on the three-way interaction of condition with ROI and group. For a complete listing of the effects and corresponding statistical values see Table 4. A repeated measures ANOVA including all four conditions revealed that the conditions produced different activation patterns in each ROI and group (interactions of condition*group and condition*ROI*group). Next, to examine the two levels of specialization for print independently, we computed three separate ANOVAs each including two conditions only, comparing the four conditions with each other.

Firstly, in order to test the VWF-system specialization for print, we compared words with visual control stimuli by computing an ANOVA with W and FF. This analysis yielded a significant interaction of condition*ROI*group ($F(4,37) = 3.1, P = .032$), indicating that the difference between W and FF is dependent on the location of the ROIs and group. *T*-tests confirmed that in the control children W produced less activation than FF in the most posterior ROI (ROI5: $t = -2.5, P = .021$), that W produced more activation than FF in the anterior ROI2 ($t = 2.5, P = .020$). By contrast, the dyslexic children showed a significant difference between W and FF only in the most anterior ROI (ROI1: $t = 2.3, P = .032$). Next, in order to clarify whether this gradient was specific to words or generalized to print, we calculated additional ANOVAs to contrast the conditions PW and FF (excluding semantic and lexical influences as confounding factors), as well as the mean of all letter string conditions (W, PH, PW) and FF (i.e., print vs. visual control stimuli). Both ANOVAs yielded a significant interaction of condition*ROI*group (PW and FF: $F(4,37) = 3.8, P = .007$; mean(W, PH, PW) and FF: $F(4,37) = 4.6, P = .003$). *T*-tests confirmed that, in controls, print evoked stronger activity than FF in all ROIs except the most posterior one (for PW vs. FF: ROIs 1 & 3 $P < .05$ and $t > 2.3$, ROI2 $P < .001$ and $t = 4.2$, except ROI4 $P < .1$ and $t = 2.0$, ROI5, n.s.; and similar for mean(W, PH, PW) vs.

FF). By contrast, the dyslexic children did not show a significant difference between print and FF in any of the ROIs, except for ROI1 (for mean(W, PH, PW) vs. FF: $t = 3.0, P = .009$). These findings provide clear evidence that a posterior-to-anterior gradient of increasing coarse print specificity is disturbed in children with dyslexia.

Secondly, in order to examine the effect of orthographic familiarity on VWF-system activation, we compared the conditions W and PH as well as W and PW. The ANOVA for W and PH revealed a significant interaction of condition*group ($F(1,40) = 5.4, P = .025$). The ANOVA with W and PW showed an interaction of ROI*group ($F(4,37) = 3.3, P = .021$). Based on our a priori interest in the VWF-system and because we wanted to verify that the effect of orthographic familiarity cannot be explained by a limited number of ROIs in the VWF-system, t-tests were calculated despite the absence of a three-way interaction involving ROI. These *t*-tests clarified that PH evoked significantly more activation than W in all 5 ROIs for the control children (Figure 3-4) (all ROIs $P < .01$ and $t > 3.0$). Conversely, the dyslexic children showed no difference between PH and W in most of the ROIs, except for ROI4 ($t = -2.5, P = .024$). The *t*-tests comparing PW and W in control children revealed significantly stronger activation for PW than W in ROIs 2-5 (ROI2 $P < .01$ and $t = 3.2$; ROI 3-5 $P < .05$ and $t > 2.6$) and a trend in ROI1 ($t = 1.8, P = .089$). Again, the children with dyslexia showed no difference between PW and W in any of the ROIs. Furthermore, the VWF-system of control children was activated more for PH than for PW in ROI4 ($t = 2.4, P = .026$) and ROI3 ($t = 2.1, P = .048$), in contrast to that of the dyslexic children (all $P > .1$).

Please insert Figure 3 & 4 approximately here

Please insert Table 4 approximately here

Discussion

The present fMRI study compared visual word processing in control children and in children with dyslexia, focussing on gradients of brain activation in the occipitotemporal VWF-system. The children with dyslexia exhibited typically poor reading performance. The behavioural results indicated that these children had problems not only with phonological decoding (phonological lexical decision task) but also with distinguishing between orthographically correctly and incorrectly written words (orthographic judgement task).

The fMRI data showed that we were able to demonstrate in a single experiment (thus controlling for general arousal levels) that reading related activity in the VWF-system can be dissociated at (at least) two functional levels in young children – i.e. print specificity and orthographic familiarity. Most importantly, the data provide two core findings supporting our main hypothesis that impaired specialization for print and automatization of word reading exists early in reading acquisition in dyslexic children and is linked to a dysfunctional VWF-system. First, we found that the posterior-to-anterior gradient of increasing print specificity, as identified in control children by contrasting letter strings (W, PH and PW) with visual control stimuli (FF), was not detectable in dyslexic readers. Second, we found that dyslexic children did not show the orthographic familiarity effect on occipitotemporal activation (i.e., higher activity for unfamiliar than for familiar word-forms) anywhere in the VWF-system.

These two core findings demonstrate that word processing deficits in dyslexic children are associated with an early impairment of two types of specialization for visual word processing subserved by the left occipitotemporal VWF-system.

Absence of Posterior-to-Anterior Gradient of Increasing Print Specificity in Dyslexic Children

Our findings for control children are consistent with previous fMRI studies in adults and adolescents since we demonstrated that FF evoked stronger activation than W in left posterior occipitotemporal cortex (Brem et al., 2006; Brem et al., 2009) and W evoked stronger activity than FF in left anterior occipitotemporal cortex (Brem et al., 2006; Brem et al., 2009; Vinckier et al., 2007), whereas W and FF evoked similar activity in the central ROI (VWFA proper) (Brem et al., 2006; Brem et al., 2009; Price et al., 1996; Tagamets et al., 2000; Turkeltaub et al., 2003). This result demonstrates that, while visual control stimuli are processed more efficiently than words in posterior regions, this preference is reversed (i.e. stronger activation for words than false fonts) in increasingly more anterior locations. These findings provide support for a posterior-to-anterior gradient of increasing specificity for words. As a novel finding, we were able to demonstrate that this gradient was not limited to words (versus FF) but generalized to other letter strings. Specifically, not only the comparison of W vs. FF but also of PW vs. FF and the mean of all letter string types (W, PH, PW) vs. FF showed increasing specificity for print vs. false-fonts from posterior towards anterior regions in control children (interaction condition*ROI*group). In the following, we will therefore refer to this gradient as the posterior-to-anterior gradient of increasing print specificity.

In contrast to control children, dyslexic children did not show differential activation for letter strings (W, PH and PW) and visual control stimuli (FF) in the

VWF-system, indicating that the posterior-to-anterior gradient is absent in dyslexics. This finding is consistent with earlier studies reporting reduced print-specific tuning of the N1 in adults with a severe form of dyslexia (Helenius et al., 1999) and in young, reading-impaired children in a similar reading test (Maurer et al., 2007). Thus, our results provide support for an impairment in the fast, coarse form of visual tuning for print in dyslexic children, which in control children may be considered a first level of specialization of the VWF-system.

Absence of Orthographic Familiarity Effect in Dyslexic Children

Next, we investigated the specialization for visual print processing more closely by examining occipitotemporal activation in response to the three letter string types, leaving out the FF stimuli. We were able to demonstrate that the effect of orthographic familiarity on the activity of the VWF-system (i.e., higher activity for unfamiliar than for familiar word-forms) is not detectable at any of the examined locations in the VWF-system of dyslexic children, except for the most anterior ROI.

The present study significantly extends previous studies (Bruno et al., 2008; Kronbichler et al., 2007; Mechelli et al., 2003) that found an effect of orthographic familiarity in adults and adolescents in two ways. First, it demonstrates that such an effect is already present in children with only a few years of reading experience. Second, we demonstrated that this effect involves profiles extending over multiple areas located along the posterior-anterior axis of the occipitotemporal VWF-system, rather than being limited to the VWFA. This pattern of activation in the occipitotemporal cortex is indicative of a specialization of this region for processing familiar letter strings. Consistent with the concept of an 'orthographic input lexicon'-function of the VWFA (Bruno et al., 2008; Kronbichler et al., 2007), we propose that the stronger activity in the occipitotemporal cortex for PH and PW compared to W is

caused by prolonged screening of the orthographic lexicon for a matching word entry. Our results therefore support the notion that the VWFA processes letter strings also at the whole-word ([i.e., word-form](#)) level (Bruno et al., 2008; Kronbichler et al., 2007). This finding contrasts with previous studies demonstrating similar activation for W and PW in the VWFA (Dehaene et al., 2002; Wydell et al., 2003) and adjacent areas (Vinckier et al., 2007), suggesting prelexical processing in the VWFA.

Unlike those studies of adults or adolescents that show that activity for PH and PW is equally increased in comparison to W, we found a significant difference between PH and PW. Our study is more careful in controlling response bias than previous studies with only three conditions (Bruno et al., 2008; Kronbichler et al., 2007; Wimmer et al., personal communication). Given that response requirements may affect activation patterns, differences in task design between the current and previous studies might also explain differences in findings between these studies for the comparison of PH (requiring a 'yes' response) and PW (requiring a 'no' response) – i.e. we found lower activity for PW than PH, whereas previous studies found no difference between PH and PW in left occipitotemporal regions (Bruno et al., 2008; Kronbichler et al., 2007). [Nevertheless, although the activation difference between PH and PW is not a focus of the present study, the design of our study as well as the previous studies mentioned above did not control for response differences between PH and PW. Future studies are necessary to compare brain activation in response to PH and PW for different response categories.](#)

Importantly, our data reveal that the orthographic familiarity effect is already present in control children after 4-5 years of reading experience, and extends over multiple regions in the occipitotemporal cortex rather than being confined to a specific region within the VWF-system (VWFA) (Bruno et al., 2008; Kronbichler et al., 2007). Some authors hypothesized that expertise increases with growing reading

experience, which may result in an increasing difference between brain responses to familiar and unfamiliar word-forms (Bruno et al., 2008). The effect of orthographic familiarity is not specific for German speakers but can be generalized to other languages as it was found to occur not only in German (Kronbichler et al., 2007) but also in English (Bruno et al., 2008) orthography. However, for the future, it would be important to examine specifically the role of orthographic familiarity in dyslexia also in deeper orthographies such as English where the effects may well be more prominent.

Finally, the finding that this occipitotemporal brain system is less sensitive to orthographic familiarity in children with dyslexia corresponds closely to the results of a recent fMRI study with dyslexic adults and adolescents (Wimmer et al., personal communication). However, in contrast to both Wimmer et al. and Shaywitz et al. (2002), we did not find a general underactivation of the occipitotemporal cortex (i.e. lower activation for all conditions in dyslexics than controls), possibly due to the fact that we examined young dyslexic children rather than adults and adolescents.

What is the Exact Nature of the VWF-System Dysfunction?

Unlike most previous fMRI studies that examined local activation differences, our approach was to examine differences in preferential processing (i.e. specialization for one stimulus type vs. another), and spatial response gradients or sensitivity profiles across multiple regions along the anterior-posterior axis of the occipitotemporal cortex in control children. This approach allowed us to reveal spatially distributed, differences concerning a meaningful functional architecture. Our finding of two types of processing in the left occipitotemporal cortex in controls is in line with the results of a priming study by Dehaene et al. (2004). First, their finding of a posterior-to-anterior gradient of increasing invariance for letter location (i.e. from location-specific representation of letters in posterior regions to location-invariant representation of

words in anterior regions) is comparable to our posterior-to-anterior gradient of increasing print specificity. Second, their finding of a case-invariant representation of letters in this region is comparable to our finding of the presence of the orthographic familiarity effect throughout the occipitotemporal VWF-system.

Subsequently, we investigated whether dyslexia affected this preferential processing. Our results suggest that the dysfunction of the occipitotemporal cortex is characterized by a disturbance in both *functional* and *spatial* organization along its posterior-to-anterior axis. We were able to demonstrate that multiple regions along the posterior-to-anterior axis of the VWF-system are affected, rather than just its well-known core area i.e. the VWFA proper. To the best of our knowledge, this is the first study to demonstrate impaired specialization of the VWF-system in dyslexic children at both coarse, low-level (print vs. visual control stimuli) and fine-grained high-level (orthographically familiar vs. unfamiliar, i.e. W vs. PH) word processing. Such deficits at multiple levels are in line with converging evidence that the occipitotemporal cortex has more than one function and responds to multiple levels of sublexical orthographical structures (Binder et al., 2006; Dehaene et al., 2002; Vinckier et al., 2007; Wydell et al., 2003). Additionally, corresponding to previous findings, this same region shows sensitivity on the whole-word level as demonstrated by the effect of orthographic familiarity (Bruno et al., 2008; Kronbichler et al., 2007; Wimmer et al., personal communication) and cross-modal priming effects (Buckner et al., 2000; Klaver et al., 2007).

While the whole brain analysis indicated a significant group difference for PH near the VWFA, the ROI analyses revealed only one significant group difference for an individual condition: for W in ROI5. This finding leads us to suggest that the impairment of the VWF-system mainly appears to involve deficient tuning, i.e. for a certain stimulus type relative to other stimulus types (e.g., letter strings vs. false-font

items, as well as familiar vs. unfamiliar word-forms) as encoded along the VWF-system, rather than a less specific, general underactivation of an occipitotemporal “skill zone” for word reading (Sandak et al., 2004; Shaywitz et al., 2002; Shaywitz et al., 2007). We therefore propose that the concept of an occipitotemporal “skill zone” should be extended to involve spatial reorganization of functional specialization (which might be especially important during the first years of reading acquisition). Possibly, due to neuroanatomical abnormalities, the occipitotemporal cortex of dyslexic individuals is impaired in developing reading expertise (Kronbichler et al., 2007; Maurer et al., 2007; Shaywitz et al., 2007). Thus, during the first years of reading acquisition, the occipitotemporal cortex might be subjected to functional and structural changes resulting in the posterior-to-anterior gradient with increasing specificity for print. Accordingly, a recent voxel based morphometric study found the left inferior occipitotemporal cortex to be one of several regions exhibiting reduced gray matter density in dyslexic adults and adolescents (Kronbichler et al., 2008). Such a dysfunction might affect both local specialization for processing print stimuli and the development of a more abstract representation of whole word units (i.e., an orthographic input lexicon) and interfere with several stages in reading acquisition. Future research on systematic changes in levels of word- and print processing in dyslexic individuals will further contribute to a deeper understanding of this impairment.

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Figure Legends

Figure 1. Activations Induced in the Left and Right Occipitotemporal Cortex and in the Whole Brain by Letter Strings and False-Fonts in Both Controls and Children with Dyslexia, Overlaid on a Surface-Rendered Single Subject Brain Normalized to MNI Template.

Comparison of BOLD activation evoked by each condition (W, PH, PW, FF) against fixation in control and dyslexic children (FDR corrected, $P < .05$, $k > 10$). (C)

Comparison of BOLD activation for control vs. dyslexic children ($P < .001$

uncorrected for multiple comparisons, $k > 10$). Axial slices show activation clusters for all conditions and groups at $z = -12$ (VWF-system) and $z = 6$ (Broca's area) – in

red: controls, yellow: children with dyslexia, green: comparison of controls vs.

children with dyslexia. Abbreviations: W: words, PH: pseudohomophones, PW:

pseudowords, FF: false-fonts.

Figure 2. Activations Induced in the Left and Right Occipitotemporal Cortex and in the Whole Brain, Revealed by Contrasting the Main Conditions in Both Controls and Children with Dyslexia, Overlaid on a Surface-Rendered Single Subject Brain Normalized to MNI Template.

BOLD activation evoked by the comparison of the letter string conditions (A) 'W vs.

FF', 'FF vs. W', (B) 'PH vs. W', 'W vs. PH' and (C) 'PW vs. W', and 'W vs. PW' in

control and dyslexic children. Regions of BOLD activation evoked by the group

comparison 'controls vs. dyslexics' for the contrasts 'FF vs. W', 'PH vs. W', and 'PW

vs. W'. Axial slices show activation clusters for all contrasts and groups at $z = -12$

(VWF-system) and $z = 6$ (Broca's area). Statistical threshold was $P < .001$

uncorrected for multiple comparisons, $k = 10$. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts.

Figure 3. ROI Analysis in the VWF-System.

BOLD response (mean percent signal change) in five consecutive regions of interest along the anterior-posterior axis of the left occipitotemporal cortex. Error bars represent 1 S.E.M. across subjects.

Figure 4. Gradient Images Illustrating the Spatial Layout of Occipitotemporal Cortex Sensitivity for Print.

Occipitotemporal sensitivity to W vs. FF (A) and W vs. PH (B) is shown. Activation maps are displayed on left ($x = -42$) and right ($x = 42$) hemispheric slices (colour bar indicates T-values with range -3 to 3) and are restricted to occipitotemporal areas (including the fusiform gyrus, calcarine fissure, occipital inferior and lingual gyrus; mask generated by Pickatlas software version 2.3 (Maldjian et al., 2003)).

Table 1. Demographic Characteristics of the Control and Dyslexic Children and Group Differences (*t*-test or chi-square).

	Dyslexic Children	Control Children	<i>P</i> -value
n	18	24	–
Age (years)	11.4 ± 0.7	11.3 ± 0.4	n.s.
Sex (male:female)	10:8	10:14	n.s.
Handedness (right:left)	15:3	17:7	n.s.
Estimated Verbal IQ	109 ± 11	114 ± 14	n.s.
Estimated Non-verbal IQ	111 ± 12	112 ± 11	n.s.
Correctly read W/min	49 ± 8	93 ± 16	<i>P</i> < .001
Correctly read PW/min	32 ± 5	54 ± 14	<i>P</i> < .001
Spelling	30 ± 23	86 ± 21	<i>P</i> < .001

Means and standard deviations (SD) are displayed; n.s.: non-significant.

Table 2. Performance During Phonological Lexical Decision Task and Item Characteristics.

Measures	W	PH	PW	FF
Task Performance				
<i>Phonological lexical decision task (fMRI)</i>				
Accuracy (%)				
Control children	94 (±7)	87 (±9)	91 (±8)	99 (±1)
Children with dyslexia	92 (±8)	80 (±9)	78 (±7)	98 (±3)
<i>p</i> -value	n.s.	<i>P</i> = .017	<i>P</i> < .001	n.s.
Reaction time (ms)				
Control children	1033 (±299)	1196 (±340)	1338 (±361)	837 (±227)
Children with dyslexia	1401 (±297)	1608 (±252)	1904 (±288)	895 (±198)
<i>p</i> -value	<i>P</i> < .001	<i>P</i> < .001	<i>P</i> < .001	n.s.
<i>Orthographical judgment task</i>				
Accuracy (%)				
Control children	93 (±19)	90 (±19)	95 (±20)	-
Children with dyslexia	90 (±5)	77 (±11)	96 (±4)	-
<i>p</i> -value	n.s.	<i>P</i> = .013	n.s.	-
Item Characteristics				
Number of characters	4.5 (± 0.7)	4.5 (± 0.8)	4.5 (± 1.0)	4.5 (± 0.7)
Bigram Frequency	11771 (± 8385)	10282 (± 9043)	11328 (± 9094)	-
Word Frequency	68.3 (± 74.2)	-	-	-

Means and standard deviations (SD) are displayed for the control, the dyslexic children and all four item types. Significant p -values indicate group differences.

Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-
fonts, n.s.: non-significant.

Table 3. Main Activation Peaks of the Reading Network in Both Control and Dyslexic Children for Each Main Comparison of the Conditions.

Contrast	Group	Region	MNI Coordinates			
			x	y	z	Z
<i>W > FF</i>	Controls	L Inferior Frontal g.	-39	21	6	5.04
		L Insula	-48	9	3	4.63
		R Inferior Frontal g.	33	27	3	3.43
	Dyslexics	L Inferior Frontal g.	-51	27	18	4.42
		R Inferior Frontal g.	39	24	-3	3.66
<i>PH > W</i>	Controls	L Superior Parietal g.	-33	-51	51	5.25
		L Inferior Frontal g.	-30	20	2	4.79
		L Fusiform g.	-48	-60	-24	4.12
	Dyslexics	L Inferior Frontal g.	-39	6	30	4.60
	<i>PW > W</i>	Controls	L Inferior Frontal g.	-51	12	21
L Fusiform g.			-42	-42	-21	3.51
Dyslexics		L Inferior Frontal g.	-48	12	21	5.44
		L Middle Occipital g.	-36	-87	3	3.22

MNI coordinates (x/y/z) are listed for local maxima of significant clusters ($P < .001$, uncorrected for multiple comparisons). Z-values are listed for voxels at the local maxima. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts, L: left hemisphere, R: right hemisphere, g.: gyrus, l.: lobule.

Table 4: ROI Analysis.

	A		B		C		D	
ANOVA:	W, PH, PW and FF		W and FF		W and PH		W and PW	
ROI	$F(4,37) = 12.18$	$P < .001$	$F(4,37) = 10.93$	$P < .001$	$F(4,37) = 9.31$	$P < .001$	$F(4,37) = 8.11$	$P < .001$
ROI * group	$F(4,37) = 2.26$	$P = .087$	-	-	$F(4,37) = 3.26$	$P = .023$	$F(4,37) = 3.29$	$P = .021$
condition	$F(3,38) = 12.20$	$P < .001$	-	-	$F(1,40) = 18.61$	$P < .001$	$F(1,40) = 16.50$	$P < .001$
condition * group	-	-	-	-	$F(1,40) = 5.40$	$P = .025$	-	-
ROI * condition	$F(3,38) = 2.07$	$P = .045$	$F(1,40) = 2.40$	$P = .072$	$F(4,37) = 2.96$	$P = .039$	-	-
ROI * condition * group	$F(12,29) = 2.16$	$P = .036$	$F(4,37) = 3.05$	$P = .032$	-	-	-	-
group	-	-	-	-	-	-	-	-

A) Repeated Measures Analysis of Variance (RM-ANOVA): 4 conditions * 5 ROIs * 2 groups; B),C),D) RM-ANOVA: 5 ROIs * 2

conditions * 2 groups. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts.

Figure 1
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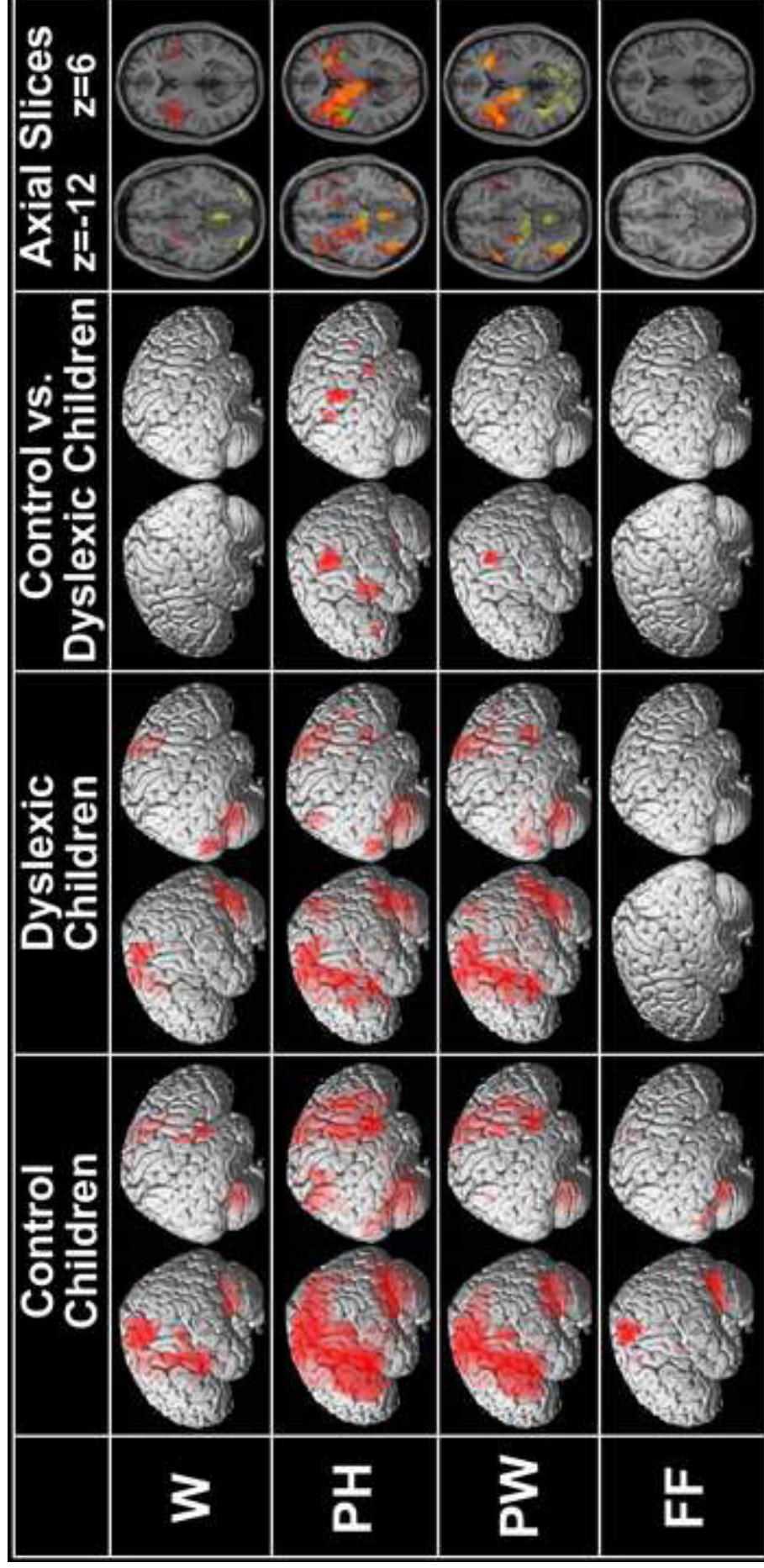


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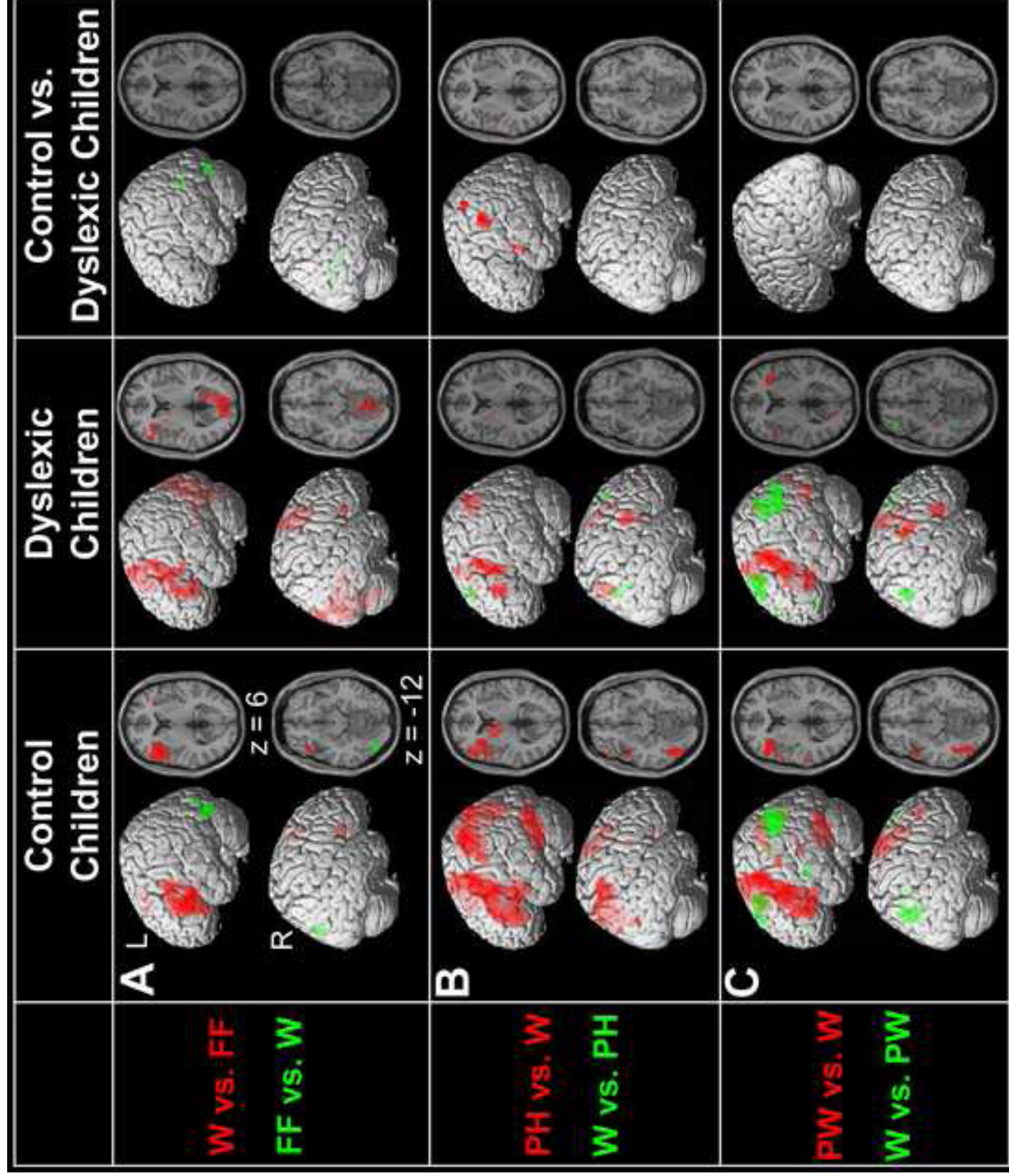


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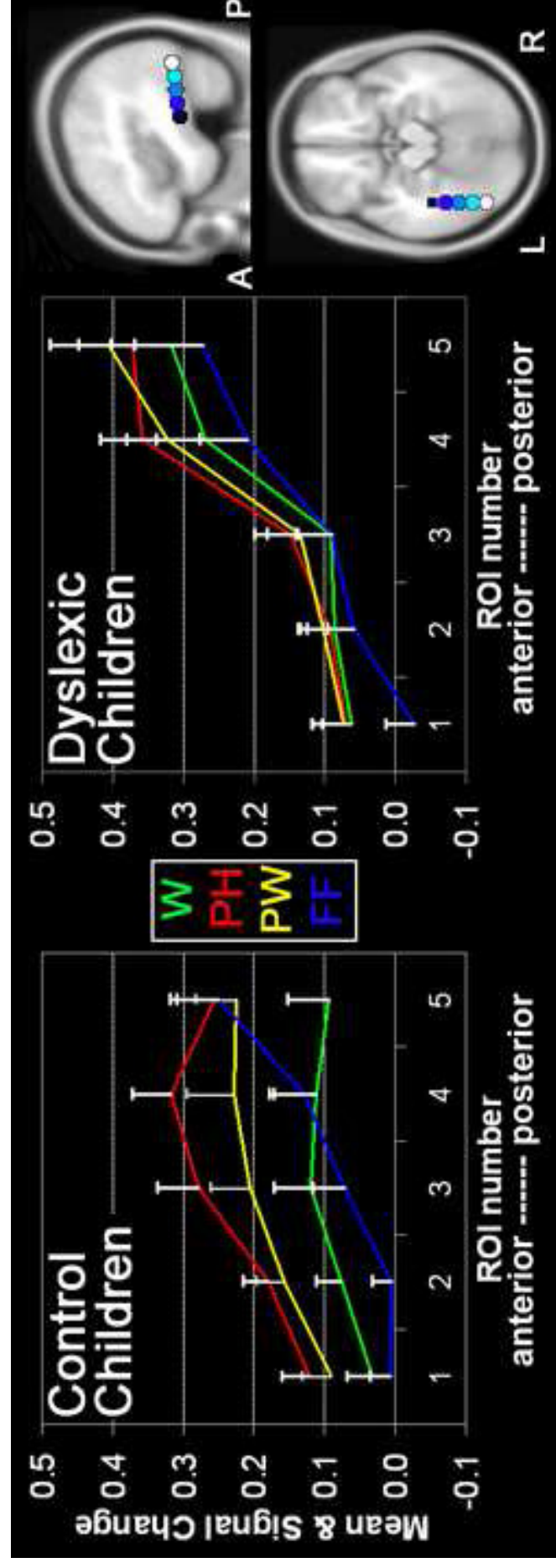
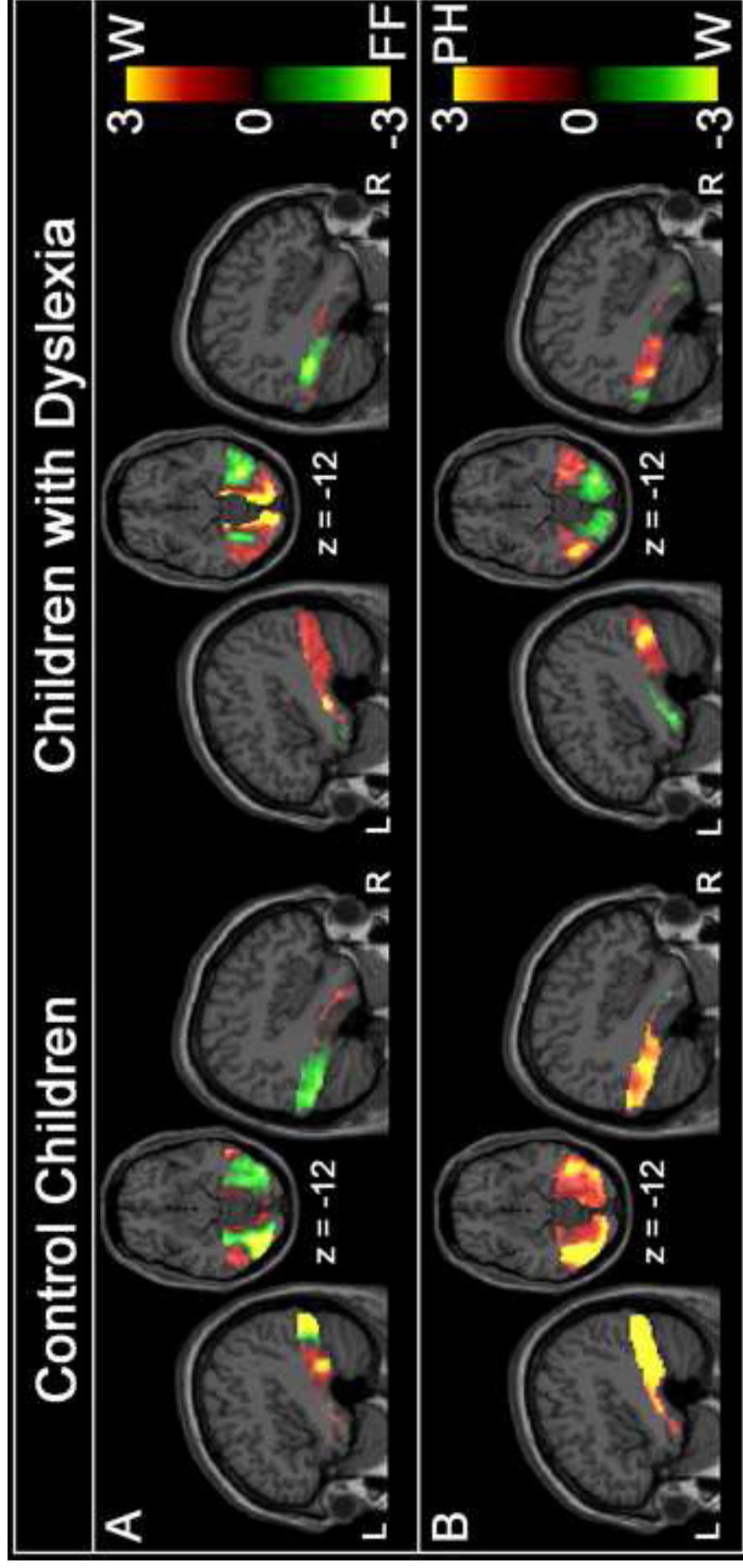


Figure 4
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6. Supplementary Material

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