

Simultaneous EEG and fMRI reveals stronger sensitivity to orthographic strings in the left occipito-temporal cortex of typical versus poor beginning readers

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ARTICLE INFO

Keywords:

Children

Reading

Simultaneous EEG-fMRI

Visual word form system

Visual N1

EEG-informed fMRI analyses

ABSTRACT

The level of reading skills in children and adults is reflected in the strength of preferential neural activation to print. Such preferential activation appears in the N1 event-related potential (ERP) over the occipitotemporal scalp after around 150–250 ms and the corresponding blood oxygen level dependent (BOLD) signal in the ventral occipitotemporal (vOT) cortex. Here, orthography-sensitive (print vs. false font) processing was examined using simultaneous EEG-fMRI in 38 first grade children with poor and typical reading skills, and at varying familial risk for developmental dyslexia. Coarse orthographic sensitivity was observed as an increased activation to print in the N1 ERP and in the BOLD signal of individually varying vOT regions in 57% of beginning readers. Finer differentiation in processing orthographic strings (words vs. nonwords) further occurred in specific vOT clusters. Neither method alone showed robust differences in orthography-sensitive processing between typical and poor reading children. Importantly, using single-trial N1 ERP-informed fMRI analysis, we found differential modulation of the orthography-sensitive BOLD response in the left vOT for typical readers only. This result, thus, confirms subtle functional alterations in a brain structure known to be critical for fluent reading at the very beginning of reading instruction.

1. Introduction

Reading remains one of the most important cultural skills in today's life and is crucial for a child's academic and personal development (Mugnaini et al., 2009; Poskiparta et al., 2003; Snowling, 2013). However, 3–10% of the children do not master the challenges of fluent reading and are diagnosed with developmental dyslexia, a developmental reading disorder (Snowling, 2013). Familial risk increases the prevalence of dyslexia to 30–65% in children of affected families (Pennington and Lefly, 2001). A better understanding of the neural alterations in the underlying functional language network in children with poor reading development and especially in children with heightened

risk shortly after school enrolment may help to provide individualized support.

The left ventral occipito-temporal cortex (lvOT) is known as a key structure for fluent and efficient reading and is therefore often referred to as the visual word form system (VWFS; (Baker et al., 2007; Centanni et al., 2018; Coch and Meade, 2016; Cohen et al., 2000, 2002; Dehaene and Cohen, 2011; Glezer et al., 2009; McCandliss et al., 2003; Price et al., 1996; Saygin et al., 2016; Vinckier et al., 2007)). Within the center of the midfusiform gyrus, lies a word form sensitive area, the “visual word form area” (VWFA; Baker et al., 2007; Centanni et al., 2018; Coch and Meade, 2016; Cohen et al., 2000, 2002; Dehaene and Cohen, 2011). Because reading is a relatively recent cultural skill, it is suggested that

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<https://doi.org/10.1016/j.dcn.2019.100717>

Received 1 April 2019; Received in revised form 23 August 2019; Accepted 1 October 2019

Available online 4 October 2019

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the VWFA has adopted a special function in the orthographic recognition of written words (Cohen et al., 2000; Glezer and Riesenhuber, 2013) within the last few thousand years (Dehaene and Cohen, 2007) through progressively tuning to process written words during reading acquisition (Brem et al., 2010, 2013; Dehaene-Lambertz et al., 2018; Maurer et al., 2005, 2011; Saygin et al., 2016). The electrophysiological correlate of the left vOT activation in early categorical processing is the visual N1 event-related potential (ERP) with its characteristic negativity over the left occipitotemporal scalp after 150–250 ms (N1, N170; Bentin et al., 1999; Brem et al., 2005; Maurer et al., 2005; Pegado et al., 2014), as evidenced by intracranial recordings (Hirshorn et al., 2016; Nobre et al., 1994), EEG-source localization (Brem et al., 2009; Maurer et al., 2005) and magnetoencephalography studies (MEG; Hirshorn et al., 2016; Tarkiainen et al., 1999).

The preferential activation to print in the left vOT develops with the start of formal reading instruction in childhood (Ben-Shachar et al., 2011; Brem et al., 2013; Cao et al., 2011; Chyl et al., 2018; Dehaene-Lambertz et al., 2018; Eberhard-Moscicka et al., 2015; Maurer et al., 2007, 2006; Saygin et al., 2016; Zhao et al., 2014) or adulthood (Dehaene et al., 2010) and seems to be initiated by letter-speech sound or letter-motor association training (Brem et al., 2010; James, 2010; Karipidis et al., 2017; Pleisch et al., 2019). Recent studies examining children from preschool onwards indicated that the process of developing functional specialization to print builds on preexisting connections between the left vOT and higher order language areas (Saygin et al., 2016) and manifests itself in previously weakly specialized cortical vOT areas (Dehaene-Lambertz et al., 2018). During reading development, the tuning to print in the N1 ERP shows an inverted U-shaped development with maximal differentiation in beginning readers (Fraga González et al., 2014; Maurer et al., 2006). While coarse tuning to orthographic processing shows an early maturation upon reading instruction in childhood (Brem et al., 2010; Chyl et al., 2018; Eberhard-Moscicka et al., 2015; James, 2010; Maurer et al., 2007), full specialization and word form selective responses (fine orthographic tuning) of the vOT typically show a more protracted development (Centanni et al., 2017). Such fine, word form selective tuning with differential activation to words as compared with other letter strings is typically not detectable in the N1 ERP of young beginning readers but may be present in children with high reading abilities (Zhao et al., 2014). Moreover, the detection of word-selective BOLD responses in the vOT may necessitate the application of highly sensitive fMRI tasks and individual localization of word-sensitive vOT regions (Glezer et al., 2009; Glezer and Riesenhuber, 2013; Lerma-Usabiaga et al., 2018).

The strength of the orthography-sensitive response in the vOT has been associated with the expertise level of reading (Ben-Shachar et al., 2011; Chyl et al., 2018; Dehaene et al., 2005; Zhao et al., 2014) and disruption of the activity in the midfusiform gyrus through stimulation led to impaired word and letter processing (Hirshorn et al., 2016). Attenuated functional activation and diminished functional connectivity (Shaywitz et al., 2002; van der Mark et al., 2011) of this region during reading tasks (for meta-analyses see Maisog et al., 2008; Richlan et al., 2009; Richlan et al., 2011) suggest a failure in orthographic processing, severely affecting the reading process. Print sensitivity and the corresponding differential vOT activation is typically reduced in poor reading children (Araújo et al., 2012; Boros et al., 2016; Brem et al., 2013; Hasko et al., 2013; Hoefft et al., 2007; Maurer et al., 2011; Richlan et al., 2011; van der Mark et al., 2009), adolescents (Kronschabel et al., 2013), and adults (Brambati et al., 2006; Helenius et al., 1999; Mahé et al., 2013, 2012; Paulesu et al., 2001; Richlan et al., 2009, 2011), as seen in ERP, MEG, or fMRI. Interestingly, such differences in print sensitivity were not evident in two ERP studies including third graders (Fraga González et al., 2014) and fifth graders with developmental dyslexia (Maurer et al., 2011). Fraga González et al. (2014) reported an even stronger N1 print sensitivity for third grade children with dyslexia as compared to peers with normal reading abilities. Whether or not a developmental delay may best explain such inconsistencies should be addressed in

further longitudinal studies. In correspondence with deviations of the left vOT function, structural neuroimaging studies (Kronbichler et al., 2008; but see Jednoróg et al., 2015) including meta-analyses (Linkersdörfer et al., 2012; Richlan et al., 2013) reported alterations in the form of a reduction of grey matter volume in the left vOT of dyslexic readers, allowing a moderate classification into dyslexic and typical readers (Tamboer et al., 2016).

Attenuation of print-tuning has typically been reported for poor readers with developmental dyslexia from the child to the adult, but also differences at preschool age have been described: A recent study suggested that genetic modulation of the cortical plasticity in the vOT (Skeide et al., 2016) pre-constrains reading outcome in preschool children. In accordance, studies indicate that an atypical print-sensitive ERP response can already be seen in preschool children with poor reading outcomes in the ERP and fMRI signal (Bach et al., 2013; Brem et al., 2013; Centanni et al., 2019, 2018; Maurer et al., 2007).

In summary, print tuning of the visual N1 ERP and the left vOT nicely reflects the level of reading experience and proficiency. Despite a recent increase in studies addressing neural changes during reading acquisition (Brem et al., 2010, 2013; Centanni et al., 2018; Chyl et al., 2018; Dehaene-Lambertz et al., 2018; Saygin et al., 2016), it is still unknown, at what pace coarse orthography-sensitive and fine (non-)word-sensitive activation develops within the first months of formal reading instruction, especially for beginning readers at familial risk for dyslexia. Previous cross-sectional and longitudinal studies most often focused on school children from the end of grade one onwards (Eberhard-Moscicka et al., 2015; Maurer et al., 2007; Zhao et al., 2014) rather than on children within the first half of the school year. Moreover, neuroimaging studies combining methods with high temporal (ERP) and high spatial (fMRI) resolution in children at risk for developmental dyslexia are lacking. Such a multimodal approach can provide more detailed insights about the development of print sensitivity and the relation between N1 responses and vOT activity in this context.

In this study, we aim to further examine the level of orthographic and word-sensitive processing in the brains of beginning readers at risk for developmental dyslexia. We refer to orthography-sensitive processing in vOT as brain activation showing a stronger response to orthographic (words, nonwords) as compared to well-matched visual, non-orthographic false font strings (Baker et al., 2007; Dehaene-Lambertz and Gliga, 2004; Dehaene et al., 2001; Eberhard-Moscicka et al., 2015; Gaillard et al., 2006; Glezer et al., 2009; Liu et al., 2008; Turkeltaub et al., 2003; Vinckier et al., 2007; Zhao et al., 2014). We furthermore refer to word- or nonword-sensitive brain responses when detecting differential activation within the orthographic conditions. It is important to note, that previous literature is not fully consistent with regard to the direction of activation when examining coarse orthography- and fine, (non-)word-sensitive tuning to print. While a majority of ERP studies (Bentin et al., 1999; Brem et al., 2009; Fraga González et al., 2014; Maurer et al., 2005) and a considerable number of fMRI studies (Baker et al., 2007; Lerma-Usabiaga et al., 2018; Vinckier et al., 2007) showed preferential activation to print vs. non-orthographic conditions in the N1 interval or VWFA in literates, several fMRI studies for example reported inverse orthographic print tuning effects. Such higher activation for control conditions in or nearby the VWFA in alphabetic and non-alphabetic languages thus suggested an influence of task demands with regard to visual processing (Ludersdorfer et al., 2013; Wang et al., 2011). The situation is even less clear when comparing word and nonword processing, for which task demands (Mano et al., 2012) may have an even higher impact resulting in either enhanced or reduced activation to words (Bruno et al., 2008; Cattinelli et al., 2013; Cohen et al., 2002; Kronbichler et al., 2007; Lerma-Usabiaga et al., 2018; Mano et al., 2012; Schuster et al., 2015).

To examine different levels of print-sensitive processing at the beginning of reading acquisition, we examined 38 children at risk for developmental dyslexia and varying reading fluency in the middle of first grade. We compare poor and typical reading children and explore

the impact of the familial dyslexia risk on print processing. The children performed a visual one-back task with words, nonwords and false font strings during simultaneous EEG-fMRI recordings to assess both coarse orthography-sensitive and fine (non-)word-sensitive neural activation.

2. Methods

2.1. Participants

43 healthy, German-speaking first-grade children at varying familial risk for developmental dyslexia were recruited for the neuroimaging and the behavioral session (middle of grade 1, school months 5–7). Five participants had to be excluded from analyses because of excessive motion ($N = 3$), or because children fell asleep ($N = 2$) during the neuroimaging session. The data of the remaining 38 children (22f, aged $7.34y \pm 0.3$, Table 1) were analyzed in the present study. The larger part of this sample ($N = 30$) was recruited at kindergarten age for a longitudinal study (Karipidis et al., 2017; Pleisch et al., 2019) from the greater area of the city of Zurich. Additional children were recruited in the middle of first grade ($N = 8$) to enlarge the group for the present analyses. Children's familial risk for developmental dyslexia varied and was estimated based on parents reading history assessed with the adult reading history questionnaire (ARHQ). The higher value of both parents was used to determine the familial risk score (for 15 children the risk came from the mother). For three children, ARHQ data of only one parent was available and used to determine their risk scores. A score > 0.3 (applied here) has originally been defined as indicating a family risk (Lefly and Pennington, 2000) but more recent work also applied more stringent cut-off scores of > 0.4 (Black et al., 2012; Chyl et al., 2018; Maurer et al., 2007). In addition, two children had siblings with formal diagnosis of dyslexia and one child was delayed in his language development.

Behavioral assessments included reading fluency (Salzburger Lese- und Rechtschreibtest, SLRT-II; Moll and Landerl, 2010), nonword repetition test (Mottier Silben; Wild and Fleck, 2013), phonological

awareness and rapid automatized naming (Test für phonologische Bewusstheit und Benngeschwindigkeit, TEPHOBE; Mayer, 2011). Behavioral assessments were performed $6 \pm 5.4d$ (range: 1-24d) before the imaging session; there was no difference in the interval between behavioral assessment and the neuroimaging session between the two reading groups ($t(36) = -0.931$, $p = 0.358$). The IQ assessment (Culture Fair Intelligence Test, CFT 1-R; Weiss and Osterland, 1997) took place 7.3 ± 0.5 month (range: 6.61–9.83 m) after the simultaneous EEG-fMRI session.

For one child, with whom the CFT 1-R score could not be conducted, the results of the Wechsler Intelligence Scale for Children (HAWIK-IV, subtest: block design; Petermann and Petermann, 2007) conducted in kindergarten (IQ estimate: 95) served as an estimation of IQ. No child was excluded due to below average IQ (< 80) and all children had normal or corrected to normal visual acuity and no neurological or cognitive impairments. One child with a diagnosis of attention deficit/hyperactivity disorder discontinued the medication for 48 h before the behavioral and the neuroimaging sessions. To verify the main findings, the core analyses were repeated without the data of this child.

18 children scoring below the 16th percentile in the averaged percentiles of word and pseudoword (SLRT-II) reading were defined as poor readers (PR), the remaining 20 typical reading (TR) children achieved an average percentile above 16 (see Table 1; Karipidis et al., 2018). The parents gave written informed consent and the children gave oral consent. The local ethics committee of the Canton of Zurich and neighboring Cantons in Switzerland approved the study. All participants received vouchers and presents as compensation.

2.2. Task design and performance analyses

During scanning, the children performed a visual one-back task with three conditions. In a block design real one- or two-syllable words (W), matched nonwords (NW) and false font strings (FF) were presented (Fig. 1). Participants were instructed to attend to the stimuli and to indicate immediate repetitions by a button press. Accuracy and reaction

Table 1
Group description of typical readers compared to poor readers.

	Typical readers (TR)		Poor readers (PR)		Test statistics
	range		range		
Sex (female/male)	10/10		12/6		
Age in years	7.3 ± 0.3	6.9-7.7	7.4 ± 0.4	6.8-8.21	$t(36) = 0.310$, $p = 0.758$
Handedness (left/right)	3/17		0/18		
Familial risk for dyslexia (ARHQ)	0.49 ± 0.17	0.26-0.75	0.51 ± 0.14	0.29-0.71	$t(36) = -0.358$, $p = 0.722$
	1/0/7/8/4*		1/1/2/5/9*		
IQ	103 ± 8	88-120	103 ± 11	84-123	$t(36) = -0.296$, $p = 0.769$
Reading related skills					
Word reading fluency perc. ^b	48.3 ± 23.2	11-99	6.3 ± 5.0	0.5-13.5	$t(20) = 8.423$, $p = 0.000^c$
Pseudoword reading fluency perc. ^b	38.1 ± 26	6-99	5.4 ± 6.6	0.5-17	$t(21) = 5.128$, $p = 0.000^c$
Word reading fluency ^a	15.41 ± 15	4-71	2.8 ± 1.8	0-5	$t(19) = 3.956$, $p = 0.001^c$
Pseudoword reading fluency ^a	18.2 ± 7.6	9-43	6.8 ± 5.3	0-14	$t(36) = 5.428$, $p = 0.000^c$
Phonological awareness ^a	23.8 ± 3.6	13-28	22.2 ± 3.4	17-28	$t(36) = 2.439$, $p = 0.020$
RAN objects/sec ^a	0.7 ± 0.1	0.52-1.04	0.6 ± 0.1	0.35-0.78	$t(36) = 2.861$, $p = 0.007$
RAN letters/sec ^a	1.2 ± 0.3	0.79-1.79	0.8 ± 0.3	0.39-1.22	$t(36) = 2.836$, $p = 0.000$
RAN numbers/sec ^a	1.1 ± 0.3	0.72-1.56	0.8 ± 0.3	0.53-1.28	$t(36) = 3.062$, $p = 0.004$
Nonword repetition ^d	38.3 ± 21.1	4-77	29.4 ± 21.5	1-75	$t(36) = 1.778$, $p = 0.084$
In-scanner one-back task performance					
Accuracy words (% correct)	66.7 ± 24.0	33-100	60.7 ± 26.7	17-100	$t(36) = 0.757$, $p = 0.454$
Reaction time words (ms)	912.5 ± 192.6	540-1350	929.6 ± 270.4	608-1507	$t(35) = -0.882$, $p = 0.384$
Accuracy nonwords (% correct)	61.8 ± 30.5	17-100	60.7 ± 24.1	33-100	$t(36) = 0.244$, $p = 0.808$
Reaction time nonwords (ms)	1083.4 ± 317.2	683-1799	1062.6 ± 255.8	593-1632	$t(32) = 0.194$, $p = 0.847$
Accuracy false font strings (% correct)	67.7 ± 24.6	17-100	70.2 ± 18.7	50-100	$t(36) = 0.657$, $p = 0.515$
Reaction time false font strings (ms)	887.3 ± 252.7	549-1561	1021.4 ± 298.5	569-1559	$t(35) = -1.746$, $p = 0.090$

Note: Values are mean \pm standard deviation. ^aRaw values, ^bPercentile scores based on age-matched local norms, ^cWelch-corrected for unequal variances/variance heterogeneity, ^dPercentile scores based on age-matched norms. ARHQ: adult reading history questionnaire (Lefly and Pennington, 2000), *indicating the risk factor of the children: affected siblings/speech delay/ARHQ (> 0.3) risk mother/ARHQ risk father/ARHQ risk both parents.

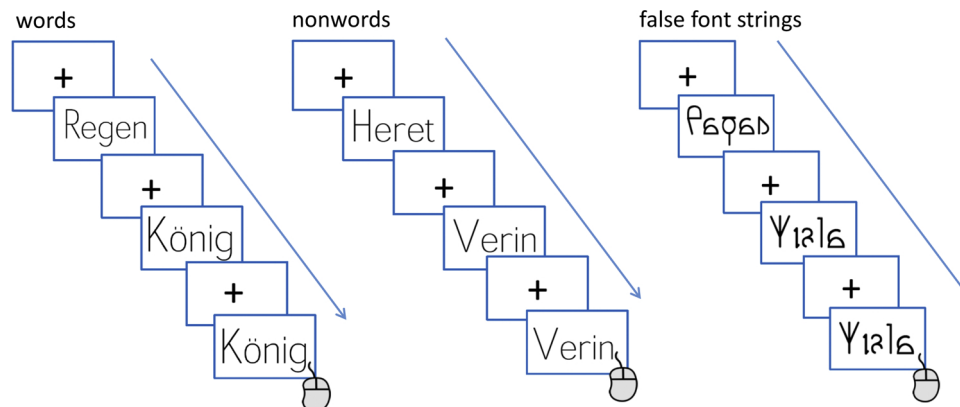


Fig. 1. Visual one-back task with three conditions: blocks of words, nonwords and false font strings were presented pseudorandomly to the children. The children had to respond to immediate repetitions of items by a button press.

time were analysed to verify children's alertness. Each false font character was created based on an alphabetical letter, by rearranging the elements into new "false font letters". With this approach, the visual appearance of letter and false font strings was closely matched. The one- or two-syllable words were concrete nouns that consisted of 3–5 letters, with the initial letter capitalized according to German orthography. The words were extracted from the German Celex database (Baayen et al., 1993) and their Coltheart-neighborhood score (Coltheart et al., 1977) ranged from 1 to 13 (mean: 5.6 ± 3.3). Pronounceable character strings with a low Coltheart neighborhood score of 0.04 ± 0.1 served as nonword stimuli. Additionally, words and nonwords were matched for bigram frequencies ($t(53) = 1,279$, $p = 0.206$; Westbury and Buchanan, 2002). The visual stimuli were presented using video goggles (VisuaStimDigital, Resonance Technology, Northridge, CA). Characters were presented in black in the middle of a grey background (mean visual angles horizontally/vertically: words: $4.3^\circ/2.0^\circ$; nonwords: $4.2^\circ/1.9^\circ$; false font strings: $4.2^\circ/1.9^\circ$). Responses and reaction times were recorded with Presentation (<http://www.neurobs.com>).

The experiment comprised 180 trials (60 per condition) and included 18 targets (6 per condition). The trials were structured in 18 blocks of 10 trials each, with either words, nonwords, or false font strings. The blocks of each condition were presented in a fixed order and the sequence of the conditions was pseudo-randomized between participants. Within each block, the stimuli were presented in a fixed order including one target. The trials started with a fixation cross (jitter: 1250–1550 ms) followed by the stimulus presentation for 660 ms. Resting periods of 6.3 s or 10.9 s were inserted between blocks. Before scanning, the children were familiarized with the experiment by performing a similar task with more target stimuli outside the scanner.

The behavioral responses from the task were analyzed for differences in accuracy and reaction time in the two reading groups. Group differences were statistically tested with unpaired t-tests.

2.3. fMRI data: acquisition

The experiment was carried out in a Philips Achieva 3 T scanner (Philips Medical Systems, Best, The Netherlands) whole body magnetic resonance scanner using a 32-elements receive head coil to acquire 254 volumes. A T2*-weighted whole-brain gradient echo-planar (EPI) sequence (echo time (TE) = 30 ms, flip angle of 80° , FOV = $24 \times 24\text{cm}^2$, in plane resolution = $3 \times 3\text{mm}^2$, SENSE factor 2.2 and SofTone factor 3) was applied recording 31 slices (thickness 3.5 mm /gap 0.5 mm) with a repetition time (TR) of 1.98 s. In order to correct for geometric distortion in EPI caused by magnetic field inhomogeneity, a field map scan to perform B0 correction was obtained before each dataset. A T1-weighted 3-dimensional magnetization-prepared rapid-acquisition echo (3D MP-RAGE) pulse sequence with 176 slices, TR = 6.8, TE = 3.2 ms,

FOV = $27 \times 25.4\text{cm}^2$ voxel size = $1 \times 1 \times 1\text{mm}^3$, and flip angle = 9° was used for segmentation and normalization.

2.4. fMRI data: preprocessing and second-level analyses

Functional images were preprocessed using SPM12 on MATLAB R2015b. Field map correction was applied. Spatial realignment to the first acquired image and unwarping was applied to correct for movements between scans and to account for distortions caused by magnetic field inhomogeneities and interpolation artifacts. Slice time correction was performed using a cubic spline interpolation. Functional images of each participant were co-registered to the corresponding T1-weighted structural image. The deformations derived from the segmentation procedure and a pediatric brain template created with the Template-O-Matic toolbox (Wilke et al., 2008) were used for the subsequent normalization. After resampling ($3 \times 3 \times 3\text{mm}^3$), a 6 mm full width half-maximum Gaussian kernel was applied to smooth the data. Volumes with more than 1.5 mm scan-to-scan movement were repaired by linear interpolation using the ArtRepair toolbox (Mazaika et al., 2011). A maximum of 8.7% of the scans per subject were interpolated.

A random-effect general linear model was calculated with five predictors (words, nonwords, false font strings, targets, and responses) for each participant and condition. Six realignment parameters were included as regressors into the model to control for head motion. First-level analyses on subject level included the contrast of each condition against baseline and the comparisons between the three conditions. Second-level random effect analyses were performed using one-sample and two-sample t-tests to characterize activation for each condition and in each group and to determine condition and group differences, respectively. Significant differences are reported using a cluster-based family wise error corrected (FWE_{corr}) threshold of $p < 0.05$ (on a cluster defining threshold (CDT) of $p < 0.001$).

2.5. fMRI data: orthography and (non-)word sensitive vOT activation

Because of individual variations in the location of potential print sensitive vOT areas in children (Centanni et al., 2017, 2018; Saygin et al., 2016) we searched for areas with print (W > FF or NW > FF) and/or (non-)word (W > NW or NW > W) sensitive BOLD responses within left/right vOT search masks using the individual (first-level) contrast images for each subject. Functional activation clusters enclosing a peak voxel surviving a voxel-wise significance threshold of $p_{\text{uncorr}} < 0.05$ and counting five or more contiguous voxels (at voxel-wise $p < 0.1$) within our bilateral vOT search masks, counted as orthography or (non-)word sensitive areas. For individuals with more than one significant activation cluster within our search masks, only the largest cluster in each hemisphere (or in the case of equally sized clusters, the

cluster with higher significance) is reported and illustrated. The bilateral vOT search masks (see Fig. 2) were defined as the combined functional activation of W, NW and FF intersected by the fusiform gyrus (aal; Tzourio-Mazoyer et al. (2002)) and had a volume of 4077 mm^3 ($= 151$ voxels) each. We derived the number of subjects exhibiting orthography, nonword- and word-sensitive activation clusters and compared i) the number of occurrence between groups, ii) the number of occurrence of nonword versus word sensitive clusters (chi square tests), and iii) potential differences in the location (mean MNI x, y, z coordinates of the clusters) of nonword- and word sensitive clusters (t-tests).

2.6. EEG data: acquisition

EEG was sampled at 1 kHz (DC) continuously with an MR-compatible 128-channel EEG system (Net Amps 400, 128-channel EGI Hydro-CelGeodesic Sensor Net) and two ECG electrodes. Impedances were kept below $50 \text{ k}\Omega$. The reference electrode was placed at Cz and the ground electrode posterior to Cz. The EEG system was synchronized to the scanner clock to minimize gradient residuals occurring during simultaneous EEG-fMRI recordings (Mandelkow et al., 2006) and the helium pump of the MR scanner was turned off during recordings to reduce vibration artefacts. A bandage retainer net covered the electrode net to reduce potential electrode vibration artifacts.

2.7. EEG data: analysis

EEG data processing was performed with VisionAnalyzer 2.1 (BrainProducts GmbH, Munich, Germany). Four electrodes with poor

data quality on the cheeks (E43, E48, E119, E120) were excluded from further processing in all subjects. Preprocessing included the following steps: Topographic interpolation of channels with poor data quality (range: 0–6 channels, mean: 2 ± 1.9 channels), visual inspection and manual exclusion of periods with major artifacts for template calculations, MR gradient artefact removal using average template subtraction (Allen et al., 2000), ballistocardiogram correction with sliding average template subtraction, filtering (0.1–30 Hz and 50 Hz Notch), down-sampling to 500 Hz, independent component analysis (ICA; Jung et al., 2000) to correct blinks, eye movements, and residual ballistocardiogram artifacts, rereferencing to the average reference (Lehmann and Skrandies, 1980), automatic artifact removal of artefacts exceeding $\pm 200 \text{ mV}$, epoching from -50 ms to 550 ms after stimulus presentation, averaging condition-wise. ERPs were calculated based on 44.5 epochs per condition (mean words: 44.3, nonwords: 44.7, false font strings: 44.5; range: 21–54 epochs). The N1 interval was defined as $\pm 30 \text{ ms}$ (184–244 ms) around the global field power (GFP) peak (214 ms) in the grand average computed over all conditions and participants. A literature-based electrode cluster (Eberhard-Moscicka et al., 2015) was used for N1 amplitude analyses and included 13 left and right occipitotemporal electrodes (LOT: E50, E57, E58, E59, E63, E64, E65, E66, E68, E69, E70, E73, E74; ROT: E82, E83, E84, E88, E89, E90, E91, E94, E95, E96, E99, E100, E101; Fig. 3). Mean N1 amplitude values of this cluster were extracted for each subject and condition and used for further analysis. Statistical analyses were performed using LMM. As descriptive analyses we also report the number of subjects per group for whom orthography- or (non-)word-sensitive N1 amplitudes were found.

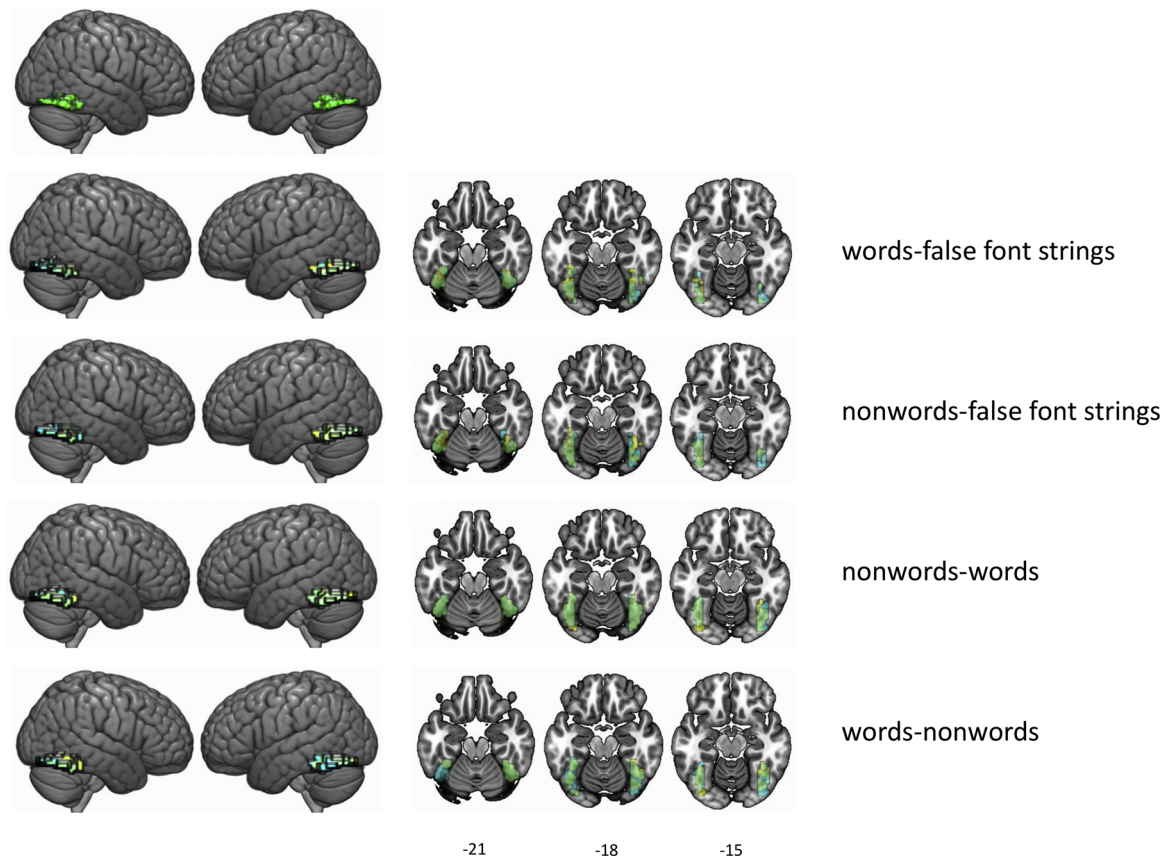


Fig. 2. Print sensitive locations: The masks (green, top left) to identify the individual print sensitive areas were defined as the cluster of functional activation over all three conditions (W, NW, FF) overlapping with the anatomically defined left fusiform gyrus (logical operation $W > \text{baseline OR } NW > \text{baseline OR } FF > \text{baseline AND } FF$) and mirrored to the right hemisphere. Depicted are the individually identified clusters for the four contrasts words-false font strings, nonwords-false font strings, nonwords-words, and words-nonwords. Clusters of typical readers (yellow) and poor readers (light blue) are shown in the render view (left) and slice (right) view (z-coordinates -21, -18, -15). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

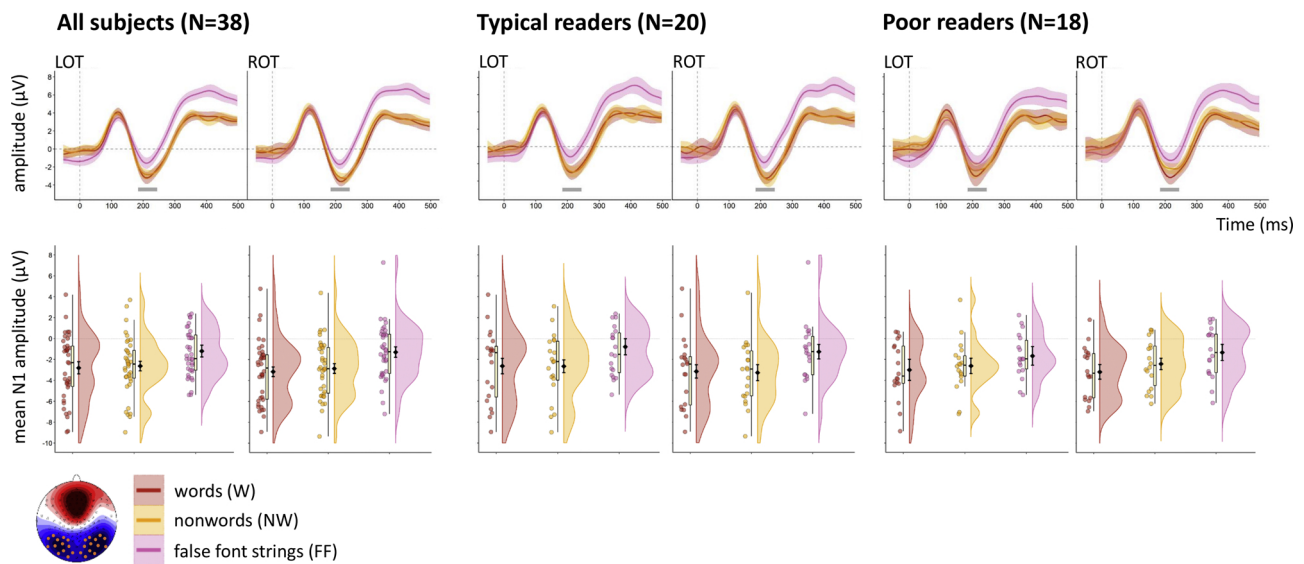


Fig. 3. Top row: ERP waveforms for all three conditions over LOT and ROT clusters for the whole group and the reading groups. Grey horizontal bars show the N1 interval (184–244 ms) defined by mean GFP peak (214 ms) \pm 30 ms. Bottom row: Mean N1 amplitudes per condition and group for LOT and ROT clusters shown in the topographical map. Error bars show 95% CI. ERP = event-related potential, LOT = left occipito-temporal, ROT = right occipito-temporal electrode clusters, CI = confidence interval.

2.8. Simultaneous EEG-fMRI data: EEG-informed fMRI analysis

To investigate how the left or right posterior occipito-temporal ERP N1 mean amplitudes modulate the BOLD response, an additional GLM for the fMRI data was defined. For this reason, the mean amplitude values of the N1 ERP over LOT and ROT for every single trial of the N1 interval (184–244 ms) were first extracted, z-transformed within each participant over all three conditions, inverted (i.e. multiplied by -1 to consider the reversed polarity of the N1 mean values (negative) and the vOT beta values (positive)) and finally entered as parametric modulators to the GLM. In this way our two (one for LOT, one for ROT) new GLMs included next to the five predictors for the three conditions (words, nonwords, false fonts), targets and responses as well as the six realignment parameters of the standard fMRI model, additionally the three parametric modulators (N1 ERP amplitude LOT or ROT) to words, nonwords and false fonts and an additional regressor of no interest to model trials with insufficient EEG quality. Finally, we also extracted the mean beta-values of this model in a priori regions of interest in the left and right vOT (Fig. 4). The vOT ROIs were defined by the intercept (logical operation OR) of 1) the combined functional activation mask of words, nonwords, and false font strings (logical operation AND) with cluster-level FWE $p < 0.05$ on a CDT of $p < 0.001$ (MarsBar; Brett et al., 2002), 2) the anatomical mask of the left or right fusiform gyrus (aal; Tzourio-Mazoyer et al., 2002) and 3) a literature-based spherical ROI (at MNI coordinates; -44/+44, -57, -15, $r = 7$ mm) described in a recent

meta-analysis on reading related activations (Vandermosten et al., 2016) representing the visual word form area (VWFA). We extracted betavalues reflecting the trial-wise parametric modulation of the LOT N1 mean amplitude with the left vOT BOLD and the betavalues reflecting the trial-wise parametric modulation of the ROT N1 mean amplitude with the right vOT BOLD. These betavalues were then entered in a linear mixed model (LMM) with fixed factors hemisphere (lvOT, rvOT), condition and group and a specific random intercept for each subject to derive condition and group differences as well as their interactions. With this method, we examined the covariation of N1 amplitudes with the BOLD signal over time in our specific regions of interest (left and right vOT).

2.9. Linear mixed model analyses of brain imaging data and correlations

As detailed in the corresponding method sections, we used linear mixed model (LMM) analyses and post-hoc t-tests (Tukey Kramer corrected) to analyze ERP N1 and single trial ERP-fMRI ROI BOLD data regarding effects of condition (W, NW, FF), hemisphere (r, l), and group (PR, TR). The random effect consists of a subject dependent random intercept. In LMM, fixed and random effects explain differences between subjects and the variability within subjects respectively. First, we used LMM models including main effects and interaction terms for all models. For all LMM models for which interaction terms were not significant, the results of the corresponding models without the interaction terms are

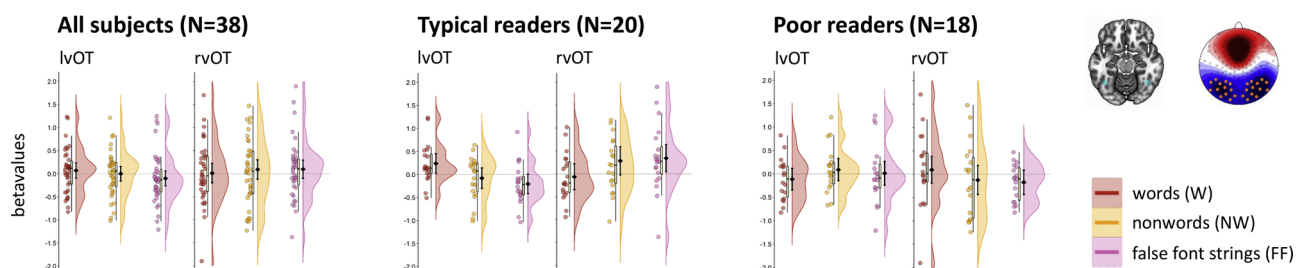


Fig. 4. EEG-informed fMRI analysis in vOT ROIs. The single-trial N1 ERP mean values modulated the hemodynamic response in the left vOT stronger for words than for false font strings in typical readers. Error bars show 95% CI. The right panel shows LOT and ROT electrode clusters (orange circles) and the a-priori-defined left and right vOT ROIs (light blue). vOT = ventral occipito-temporal, ERP = event-related potential, ROI = region of interest, LOT = left occipito-temporal, ROT = right occipito-temporal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported. For all LMM analyses, studentized conditional residuals were computed to identify and exclude potential outliers. To correct for variance inhomogeneity, an outlier cutoff of three standard deviations from the mean was used for all analyses (Roth et al., 2007). In addition, QQ-plots were inspected to ensure the assumption of normality and homoscedasticity of predicted versus conditional residual plots. All p-values of post hoc analyses are Tukey-Kramer corrected. In addition to the group analyses, we also computed correlation analyses of the word reading fluency raw score and the familial (ARHQ) risk score with all neuroimaging core measures (orthographic sensitivity: N1 mean amplitude W-FF LOT and ROT; single trial ERP-fMRI ROI beta values W-FF, see Table S1). Note, none of these correlation analyses indicated a statistical trend or significant effect and the results are thus not further

discussed.

3. Results

3.1. Behavioral data

The behavioral analyses of the reaction time and accuracy in the one-back repetition detection task yielded no difference between the reading groups (mean accuracy = 60%±5; $p > 0.139$; mean reaction time = 978 ms ± 72; $p > 0.253$; Table 1).

Table 2

MNI coordinates and anatomical labels (aal; Tzourio-Mazoyer et al. (2002)) are given for the voxel of maximal activation within each cluster for all the three conditions against baseline and the condition differences (CDT $p < 0.001$, $k \geq 44$, $FWE_{corr} p < 0.05$).

p(FWE-corr)	k	T	MNI coordinates x y z			Hemisphere	Brain region
words							
0.00000	900	10.64	-41	-87	-9	l	inferior occipital gyrus
0.00000	926	8.98	40	-87	-9	r	inferior occipital gyrus
0.00019	138	8.66	31	21	6	r	insula
0.00000	617	7.57	10	9	51	r	superior motor area
0.00168	100	7.14	-29	27	3	l	insula
0.00069	115	5.78	43	33	33	r	middle frontal gyrus
0.00012	147	5.60	28	-57	45	r	angular gyrus
0.00377	87	5.38	-29	-54	48	l	inferior parietal gyrus
0.00001	196	5.27	-44	0	30	l	Precentral gyrus
nonwords							
0.00000	1100	8.85	-26	-93	-3	l	inferior occipital gyrus
0.00000	291	6.24	-5	6	57	l	superior motor area
0.00005	149	5.99	28	-69	39	r	superior occipital gyrus
0.00000	209	5.83	-44	0	27	l	Precentral gyrus
0.00369	81	5.35	43	33	36	r	middle frontal gyrus
0.00000	223	5.25	-26	-72	30	l	middle occipital gyrus
0.04349	48	4.65	34	21	6	r	insula
false font strings							
0.00000	1294	11.28	43	-69	-6	r	inferior temporal gyrus
0.00000	1252	10.77	-41	-69	-12	l	inferior occipital gyrus
0.00000	364	6.27	31	-66	54	r	superior parietal gyrus
0.00006	157	5.24	-26	-72	30	l	middle occipital gyrus
0.00145	101	5.09	-11	15	45	l	superior frontal gyrus
words > false font strings							
0.00000	190	6.70	-53	-6	48	l	postcentral gyrus
0.00003	149	6.65	-59	-39	6	l	middle temporal gyrus
0.00000	239	5.83	-5	3	63	l	superior motor area gyrus
0.01837	55	4.72	-50	15	-3	l	inferior frontal gyrus
nonwords > false font strings							
0.00000	254	6.15	-56	3	21	l	precentral gyrus
0.02304	57	4.76	-65	-27	3	l	middle temporal gyrus
false font strings > words							
0.00000	668	8.16	43	-60	-12	r	inferior temporal gyrus
0.00000	346	6.15	-50	-66	-3	l	middle temporal gyrus
0.00032	110	5.42	52	-27	42	r	postcentral gyrus
0.04708	44	4.44	37	-75	45	r	angular gyrus
0.01997	54	4.44	19	-78	57	r	superior parietal gyrus
false font strings > nonwords							
0.00000	809	8.60	40	-60	-9	r	Inferior temporal gyrus
0.00000	222	6.61	-53	-69	-3	l	Inferior occipital gyrus
0.00209	91	5.75	61	-24	45	r	supramarginal gyrus
0.01704	61	5.00	-41	-27	48	l	postcentral gyrus
0.03133	53	4.92	-29	-39	-18	l	fusiform gyrus
0.04287	49	4.76	25	-78	57	r	superior parietal gyrus
words > nonwords							
no suprathreshold clusters							
nonwords > words							
no suprathreshold clusters							

Note: l = left hemisphere, r = right hemisphere, MNI = Montreal Neurological Institute, k = cluster size.

3.2. Whole brain differences between conditions and groups

The functional brain imaging data showed that both groups activated the occipitotemporal cortex including the left vOT (Fig. S1) during visual processing in all conditions. In addition, orthography-sensitive activation was found in the left hemisphere including the left inferior frontal, and superior and middle temporal regions (words/nonwords > false font strings). False font strings showed increased activation in the bilateral vOT and inferior parietal cortex as compared to words/nonwords (false font strings > words/nonwords, Table 2). These effects were evident in the whole sample and in both the poor and typical reading group (Fig. S1). No significant differences were observed for processing words and nonwords. Two-sample t-tests revealed no significant differences between the two groups in any condition or condition difference at the chosen, cluster-level corrected threshold of $p < 0.05$ (Fig. S2).

3.3. Orthography and (non)-word sensitive processing in the left and right vOT

Orthography-sensitive processing: Inspection of individual contrast images revealed that 57.9% ($N = 22$) of all children showed an area in the left and/or right vOT VWFS with orthographic sensitivity (for $W > FF$ or $NW > FF$: TR 60%, PR: 55.6%). The number of children exhibiting orthography sensitive areas did not differ between the groups ($\chi^2(1, N = 38) = 0.0768$, $p = 0.781$). Most of these children showed orthography sensitive areas in the left and right vOT ($N = 14$, 63.6%, TR: $N = 10$, PR: $N = 4$), six children (27.3%, TR: $N = 3$, PR: $N = 3$) only in the left and two poor reading children (9.1%) only in the right hemisphere. The mean coordinates of the orthography sensitive areas were located at MNI (x, y, z) = -39, -64, -19 in the left and at MNI 39, -63, -19 in the right vOT.

Word-/Nonword-sensitive processing: When examining the individual differences in the BOLD signal of the contrasts $W > NW$ and $NW > W$ in bilateral vOT search masks, 68.4% ($N = 26$, TR: $N = 12$, PR: $N = 14$; mean MNI (x, y, z) coordinates left: -39, -60, -18; right: 40, -62, -18) of the beginning readers showed an area with higher BOLD signal for nonwords than words. Significantly fewer children (36.8%, $N = 14$, TR: $N = 6$, PR: $N = 8$; mean MNI (x, y, z) coordinates left: -38, -55, -19; right: 40, -59, -18) showed an area with stronger BOLD for words than nonwords within the vOT ($\chi^2(1, N = 76) = 7.6$, $p = 0.0058$). The number of children exhibiting nonword- ($\chi^2(1, N = 38) = 1.3858$, $p = 0.239$) or word- ($\chi^2(1, N = 38) = 0.8495$, $p = 0.357$) sensitive areas did not differ between the typical and poor reading groups. The location of the nonword- and word-sensitive clusters in the left and right vOT did not differ significantly (for all coordinates (x, y, z) in left and right vOT $p > 0.16$). There was no indication of a preferential lateralization of word- or nonword-sensitive areas in the vOT: the number of children that showed (non-)word sensitive areas in bilateral vOT, in only the left or in only the right vOT was similar (nonword sensitive clusters: bilateral $N = 10$, only left: $N = 7$, only right $N = 9$; word sensitive clusters bilateral $N = 4$, only left: $N = 4$, only right $N = 6$).

3.4. ERP N1 amplitude analyses

ERP data showed a pronounced bilateral occipitotemporal negativity in the potential field maps after 200 ms (N1) for words and nonwords while the N1 for false font strings was less pronounced (Fig. S3). LMMs for ERP analyses were computed without interaction terms (all interactions $p > 0.11$). Analysis of the GFP confirmed the overall difference in the N1 strength by showing a significant main effect of condition [$F(2,74) = 6.31$, $p = 0.0030$] but no effect of group [$F(1,74) = 0.31$, $p = 0.5767$]. Post hoc t-tests revealed a stronger N1 GFP for words ($t(74) = 3.46$, $p_{\text{corr}} = 0.0025$) or nonwords ($t(74) = 2.42$, $p_{\text{corr}} = 0.0472$) as compared with false font strings but similar processing for words and nonwords ($t(74) = 0.15$, $p_{\text{corr}} = 0.5497$).

The amplitude analysis of the left and right occipitotemporal electrode clusters revealed a main effect of condition [$F(2,187) = 25.61$, $p < .0001$], but no significant effects of hemisphere [$F(1,187) = 1.07$, $p = 0.3015$] and group [$F(1,187) = 0.01$, $p = 0.9271$]. Post hoc t-tests confirmed the pronounced coarse orthographic sensitivity effects ($W > FF$: ($t(187) = -6.6$, $p_{\text{corr}} < .0001$); and $NW > FF$: ($t(187) = -5.7$, $p_{\text{corr}} < .0001$) but did not provide evidence for fine, word sensitive activation to words (W vs. NW : ($t(187) = -0.90$, $p_{\text{corr}} < 0.6413$); Fig. 3 and Fig. S4). Inspection of individual mean N1 amplitudes revealed that more than 86% of the children yielded coarse orthographic sensitivity (with words more negative than false font strings over LOT or ROT: TR = 90.0%, PR = 83.3%; nonwords more negative than false font strings TR = 85%, PR = 86.9%), while 71.7% of all children showed more negative amplitudes in the N1 to words as compared to nonwords over LOT or ROT (TR = 60%, PR = 83.3%) and 62.5% of the children showed more pronounced amplitudes to nonwords than words over LOT or ROT (TR = 75%, PR = 50%).

3.5. N1 ERP informed fMRI analysis in the left vOT ROI

The LMM with factors hemisphere (lvOT, rvOT), condition (W, NW, FF) and group (TR, PR) yielded a significant three-way interaction (group x hemisphere x condition [$F(2,177) = 8.75$, $p = 0.0002$]) but no main effects or two-way interaction (all $ps > 0.13$). To examine the three-way interaction in more detail we conducted two separate LMMs for each hemisphere, each including the factors group and condition. The LMM for the left vOT-N1(LOT) amplitude ERP informed parametric modulation showed a significant condition x reading group interaction [$F(2,72) = 4.23$, $p < 0.0183$] but neither main effects of group [$F(1,72) = 0.01$, $p = 0.9095$] nor condition [$F(2,72) = 1.09$, $p = 0.3415$]. Typical readers showed stronger beta-values for words than for false font strings ($t(72) = 2.97$, $p_{\text{corr}} = 0.0453$) but no difference between nonwords and false font strings ($t(72) = 0.83$, $p_{\text{corr}} = 0.9600$) or words and nonwords ($t(72) = 2.13$, $p_{\text{corr}} = 0.2833$) in posthoc t-tests. Poor readers showed no differences between conditions (all $p > 0.79$, Fig. 4). Inspection of individual N1 amplitude modulated lvOT/rvOT beta values showed that 52.6% ($N = 20$) of all children had a positive beta value to words and stronger beta values to words than false font strings, whereby this pattern of activation was present in 70.0% of typical ($\Delta N1\beta W > FF$ for all TR($N = 20$) = 0.45 ± 0.62) and 33.3% of the poor ($\Delta N1\beta W > FF$ for all PR($N = 18$) = -0.13 ± 0.70) readers. A chi-square test of independence indicated that typical reading children showed more often orthographic tuning than poor reading children ($\chi^2(1, N = 34) = 5.67341$, $p < 0.01722$). The LMM for the right vOT-N1(ROT) amplitude ERP informed parametric modulation also showed a significant condition x group interaction [$F(2,72) = 3.38$, $p < 0.0395$], a trend for a main effect of group [$F(1,72) = 2.82$, $p = 0.0975$], indicating an overall stronger BOLD in TR than PR, and no significant effect of condition [$F(2,72) = 0.15$, $p = 0.8606$]. None of the posthoc t-tests survived Tukey Kramer correction in the right hemisphere (all $p > 0.19$, Fig. 4). We therefore omitted the exploratory analyses on the individual occurrence of orthographic sensitivity over the right hemisphere.

4. Discussion

In this study, we examined whether coarse, orthographic and fine, (non-)word-sensitive processing is evident in the occipitotemporal N1 ERP amplitudes and the corresponding BOLD signals of the vOT at an early learning stage in first grade children. We also investigated whether such fine and coarse levels of print sensitive processing differ between typical and poor beginning readers at risk for developmental dyslexia. To this end, children that received half a year of formal reading instruction performed an implicit word, nonword and false font processing task during simultaneous EEG-fMRI recordings. This experiment also allowed us to further clarify the relation between N1 amplitudes over the occipitotemporal scalp and the BOLD signal within the vOT.

4.1. Coarse orthographic sensitivity in the occipitotemporal cortex and the visual N1

On a whole brain level, stronger BOLD responses to print than false font strings were mainly detected in brain areas of the left hemisphere and included inferior frontal, superior and middle temporal regions, which are part of the reading network (Perfetti et al., 2007; Price, 2012; Raschle et al., 2012; Richlan et al., 2011; Ziegler and Goswami, 2005). In our group of beginning readers, orthography-sensitive BOLD responses were detected in specific areas of the ventral occipitotemporal cortex in more than 57% of the children. This indicates that the majority of children already possesses specific orthography-sensitive areas even though the whole brain analysis mainly pointed to pronounced false font activations in bilateral vOT. This result is partly in accordance with the findings of Chyl et al. (2018) who found the emergence of print sensitive responses in the BOLD signal of the left VWFA after children mastered basic skills of reading. In convergence with our BOLD signal results and with previous ERP studies (Eberhard-Moscicka et al., 2015; Zhao et al., 2014), coarse orthographic tuning, i.e., print vs. false font, over the left occipito-temporal scalp in the N1 interval was strong and it was detected in more than 78% of all children after half a year of formal reading instruction (Brem et al., 2010; Maurer et al., 2007).

By comparing children with higher and lower familial risk scores and typical or poor reading skills, we aimed to clarify whether the vOT and N1 tuning to print are modulated by familial risk scores and reading skills. First, none of the N1 and vOT ERP-fMRI analyses revealed any significant correlation with the severity in the familial dyslexia risk score (see Table S1). Several previous ERP and MRI studies reported differences in brain structure or function between children with and without familial risk in various parts of the language system (for review see: Vandermosten et al., 2016), including reduced activation in occipitotemporal areas during phonological processing (Raschle et al., 2012). However, we did not find an association between the severity of the risk score and activation of the vOT and the N1 ERP within our at-risk sample. Further examinations in larger samples and including more low-risk and no-risk children are necessary to clarify whether familial risk scores modulate vOT responses and to disentangle the specific contribution of maternal and paternal risks (Black et al., 2012). Second, both the separate analysis of the N1 ERP and the whole-brain BOLD activation patterns did not show reduced orthographic sensitivity in poor reading children after half a year of reading instruction. Nor did we find a difference in the number of children exhibiting orthography sensitive vOT areas. In contrast to findings in more experienced readers (Araújo et al., 2012; Hasko et al., 2013; Maurer et al., 2011), these results suggest that neural differences between typical and poor readers in the vOT may not be very robust at this early stage of reading acquisition. Interestingly and similar to the findings of enhanced activation to symbol strings compared with words in medial, ventral occipito-temporal areas of beginning readers in the study by Chyl et al. (2018), the whole brain analyses yielded higher activation to false font strings than to words and nonwords in both groups over extended bilateral ventral occipito-temporal regions. Such inverse word-likeness effects with stronger activation to false font strings relative to words have been reported in studies with adults using one-back tasks (Ludersdorfer et al., 2013; Wang et al., 2011). These effects were interpreted as a sign for more effortful visual memory encoding processes for meaningless and unfamiliar false font strings (Ludersdorfer et al., 2013; Wang et al., 2011). Such demanding memory processes might have a stronger impact on the sustained activity reflected by the vOT BOLD signal (activation accumulated over several seconds) than on the temporally highly resolved and transient ERPs. Alternatively, such an inverse word-sensitivity effect may also be explained by a transient stage in the early development of print specialization (Cantlon et al., 2011). Emerging specialization of the left vOT to print has been associated with a reduction of the activation for irrelevant rather than an increase of activation for relevant categorical information (Cantlon

et al., 2011). Accordingly, the stronger activation for false font strings may indicate a developmental delay in the level of print specialization in our special group of children at risk for dyslexia. However, in contrast to the study of Cantlon et al. (2011) with preschool children, our school children showed this inverse word effect over both hemispheres, were considerably older and in a more advanced reading stage. Importantly, our individual search for print sensitive areas within the vOT, yielded in the majority of the children areas with preferential activation to orthographic conditions. While (by definition) all areas specialized for print processing in the current study were located within the VWFS or its right hemispheric homologue, the locations of these areas showed large individual variability in correspondence with previous studies (Dehaene-Lambertz et al., 2018; Saygin et al., 2016). As previously suggested, high inter-subject variability in the location and possibly also the size of specialized areas may be overlooked when only applying group level, whole-brain-based approaches or when relying on literature or functional ROI definitions that do not account for such variability (Glezer and Riesenhuber, 2013). The presence of individual print sensitive areas in our beginning readers thus clearly confirms the necessity for approaches taking into account such individual differences to capture small, functionally specialized brain areas. The result of the predominant false font activation dominating the whole brain analysis may thus best be explained by an inverse orthographic sensitivity effect that is caused primarily by task demands and which involves spatially distributed vOT patches with emerging specialization.

To further clarify the role and level of specialization of the vOT at this initial learning stage, we directly examined the modulation of the bilateral vOT BOLD signal through the N1 amplitude variations by applying a single trial ERP-informed BOLD analysis. It is well known that fMRI responses reflect a rather stationary signal, cumulating activation of the same region over several seconds and that the same brain region can repeatedly be activated during the time course of visual information processing (Dale et al., 2000; Hirshorn et al., 2016; Lin et al., 2006; Liu et al., 2002). The role of the left vOT in implicit and rapid processing of print information (within the first few hundred milliseconds and, more specifically, around the time of maximal N1 activity) may thus be superimposed by the stationary characteristics of the BOLD signal. The parametric modulation of the BOLD signal in the vOT with the N1 amplitude helps to characterize the BOLD signal covarying with the amplitude variations in a specific time interval of interest. Importantly, coarse orthographic sensitivity in the BOLD signal, modulated by the LOT N1 amplitude, was only detected in the left vOT of typical readers. More than two thirds of the typical readers, but only one third of the poor reading first graders showed such coarse orthographic sensitivity, as reflected by a higher covariation of the neural responses to words relative to false font strings in the parametric modulation of the left vOT BOLD signal. The effect of condition in this ERP-informed fMRI analysis might reflect a pattern of neural responses that is somewhat more sluggish in the temporal and/or spatial domain for false fonts vs. words. The lack of evidence for this word-false font discrimination in the group of poor readers may be another indicator of visual specialization deficits in that group. We therefore interpret the ERP-informed fMRI results as supportive of more refined specialization for fast word processing in typical readers' vOT as compared to poor readers.

Overall, the results of our study are in accordance with previous studies (Brem et al., 2010; Dehaene et al., 2010; Eberhard-Moscicka et al., 2015; Maurer et al., 2007; Skeide et al., 2017) in showing that the vOT starts to rapidly adapt to functions of reading with the start of reading training or formal reading instruction (Chyl et al., 2018; Dehaene-Lambertz et al., 2018; Maurer et al., 2005; Saygin et al., 2016; Shaywitz et al., 2002). Training, practice and the resulting increase in expertise are accompanied by important changes in neural networks detectable with sophisticated neuroimaging techniques. It remains to be clarified whether the reduced neural specialization found in poor readers is a persistent impairment (Mahé et al., 2012) or rather a developmental delay and will eventually adapt to the level of typical

readers with more practice (Araújo et al., 2014; Fraga González et al., 2014; Maurer et al., 2011).

4.2. (Non-)word-sensitive activation clusters in the vOT

Our experimental paradigm did not only allow us to explore the level of coarse orthographic print tuning in participants but also to look at differential processing between words and nonwords. While in general, a relatively late development of fine level word tuning within the left vOT is assumed (Centanni et al., 2017, 2018; Kronschnabel et al., 2013), one ERP study reported word-sensitive responses in young children with high reading abilities using a similar implicit reading task (Zhao et al., 2014). The N1 amplitude in our beginning readers did not show any differentiation between words and nonwords, neither did the whole brain analyses point to activation differences within the vOT or any other brain area. Interestingly, when searching for individual regions with word/nonword sensitive activation within the vOT, areas with differential activation to nonwords and words could be identified in 87% of the children. More than two thirds of all children (68%) exhibited areas with stronger activation to nonwords and only 37% showed some clusters with stronger activation to words than nonwords. Similar to the overall enhanced activation to false fonts in the vOT, the higher occurrence of stronger BOLD to nonwords than words may reflect increased resources and thus higher short term memory demands needed to memorize and/or process the unfamiliar nonwords in the one back task as compared with familiar word forms (Ludersdorfer et al., 2013; Wang et al., 2011). This result is still intriguing as it shows that the gained familiarity, after only half a year of reading practice at school, already facilitates visual encoding and processing of real words within specific vOT areas. In relation to this, a recent intracranial electrical stimulation study suggested the involvement of the left vOT in at least two temporally distinguishable processing stages: an early stage that allows for category-level word decoding and corresponding to the visual N1 ERP, and a later stage supporting visual (whole) word recognition (Hirshorn et al., 2016). The absence of nonword-sensitive N1 amplitudes suggests that this form of word tuning in the vOT may reflect later, probably less automatic processing stages not covered by the N1 interval. A recent fMRI study in adults further suggested a functional segregation of the left vOT into a posterior part, responsible for visual feature extraction, and an anterior part involved in integrating information from and to the language network (Lerma-Usabiaga et al., 2018). The authors ascribed activity resulting from the contrast of real words vs. false fonts as well as real words vs. pseudowords/consonant strings to the anterior “lexical” VWFA (coordinates: $x=-41$, $y=-58$, $z=-10$). In accordance with the results from Lerma-Usabiaga et al. (2018), we did not find any significant differences in the location of orthography- or (non-)word-sensitive responses; the mean coordinates of orthography sensitive ($W > FF$: $x=-39$, $y=-65$, $z=-18$; $NW > FF$: $x=-39$, $y=-64$, $z=-19$) and nonword-sensitive ($NW > W$: $x=-39$, $y=-59$, $z=-17$) clusters lied within similar positions though slightly more ventral to the reported “lexical” VWFA. Although some regions within the vOT already show a certain sensitivity for word processing, our results rather support a later maturation of early, implicit (non-)word-sensitive responses, that follows the establishment of coarse, orthographic print tuning, in children at risk for developmental dyslexia.

4.3. Limitations

Several limitations of the present study should be mentioned. First, we studied a sample of children all having a risk for developmental dyslexia. The absence of expected attenuation of orthographic sensitivity in the N1 ERP and vOT BOLD measures of poor readers and the somewhat unexpected bilateral activation pattern in both measures might be explained by the focus on children at heightened familial risk for developmental dyslexia. Although this population is of particular interest to understand functional and dysfunctional specialization of the

vOT, the exclusive focus on at-risk children raises the question of how representative our results are for the general population, given the previous reports of brain and behavioral differences in at-risk children even before the start of formal education (Dębska et al., 2016; Karipidis et al., 2017; Raschle et al., 2011; Specht et al., 2009; Yamada et al., 2011). It has been previously shown that children at risk for dyslexia or children with poor reading outcomes at preschool age show micro-structural alterations (Raschle et al., 2011), altered functional BOLD signals in tasks requiring phonological processing (Black et al., 2012; Raschle et al., 2013), grapheme-phoneme matching (Karipidis et al., 2018) or letter processing (Centanni et al., 2018), and altered N1 ERPs (Bach et al., 2013; Brem et al., 2013; Maurer et al., 2007) as compared to peers. Here, we should note that the severity of the dyslexia risk score in both our groups did not differ and none of our core ERP and BOLD measures showed significant correlations with the familial risk score. Still it is possible that children with typical reading abilities and without familial risk may show different patterns of activation, such as for example early development of fine-level differentiation between word and nonword processing in the N1 ERP (e.g. Zhao et al., 2014). Secondly, our sample includes three left-handed children. In view of reports of higher incidence of right dominant and bilateral language networks in left-handed individuals (Szaflarski et al., 2002) we repeated the main analyses after exclusion of those data and our main effects remained unaffected. Thirdly, we identified the orthography- and nonword-sensitive vOT areas based on the functional activation differences between conditions. Previous studies defined the individual VWFA location by comparing words or letters to faces (Centanni et al., 2017, 2018; Glezer et al., 2009), objects (Glezer et al., 2009; Krafnick et al., 2016) or other visual categories (Lerma-Usabiaga et al., 2018) using functional localizer tasks or partly independent categorical contrasts. The reading age of our children and the visual similarity between the contrasted string conditions may partially explain the relatively low occurrence of orthography sensitive areas in the current study. Finally, we examined children at a very early learning stage, after only half a year of formal reading instruction. This increases the risk for misclassification of the participants as poor or typical readers because the reading level also depends on teaching methods and progress at school. This may also partly explain the absence of correlations with reading fluency scores or group effects, in contrast to similar ERP/fMRI studies (Boros et al., 2016; Maurer et al., 2005, 2006; Maurer et al., 2003; Shaywitz et al., 2003; van der Mark et al., 2009). Grouping the children based on reading scores at a later stage (i.e. dyslexia diagnosis at the end of second or third grade), would be helpful to identify those children with a poor reading outcome in the longer term and to clarify potential (neural) predictors of reading outcome at this early stage.

4.4. Conclusion

In conclusion, we were able to show that children at varying risk for developmental dyslexia exhibit coarse orthographic sensitivity in the N1 ERP and in individual, specific patches of the bilateral vOT BOLD activation after only half a year of schooling. Importantly, the vOT areas with preferential activation to print categories could only be captured when taking the inter-individual differences in their location into account. Even though neural differences between typical and poor readers are not yet as prominent or robust as in more experienced readers, a refined analysis combining ERP and fMRI measures within the left vOT was sensitive enough to detect differences in the initial functional specialization to character strings between groups. These single trial ERP-informed BOLD analyses revealed that the modulation of the BOLD signal in the left vOT by the N1 amplitude is stronger for words than false font strings in typical, but not in poor reading children, suggesting more advanced orthographic tuning in the former group. Thus, besides highlighting the importance of cortical specialization to print, the ERP-informed BOLD results support that the combination of neuroimaging methods may be more sensitive to capture small but important

functional differences of specific networks in the developing brain. Our findings of reading-level-dependent sensitivity to print in a brain structure known to be critical for efficient and fluent reading from the very beginning of reading instruction, therefore, call for early identification and supportive training for children at risk for developmental dyslexia.

Declaration of Competing Interest

The authors declare no competing financial interests regarding the results of this manuscript. Susanne Walitzka has received lecture honoraria from Opopharma in the last 5 years. Her work was supported in the last 5 years by diff. EU FP7s, Hochspezialisierte Medizin of the Kanton Zurich Switzerland, Bfarm Germany, Zinep.

Acknowledgements

We thank T. Aegerter, F. Aepli, F. Mergen-Felten, L. Götze, M. Hartmann, M. Schneebeli, S. Suter, and M. Raith for their assistance during recruitment, investigation, and data analyses. We are grateful to P. Stämpfli for the technical support of MRI recordings. We thank D. Willinger and G. Fraga González for their help with the revised figures and for giving helpful advice on the new version of the manuscript. This study was supported by the Swiss National Science Foundation (grant: 32003B_141201), the Hartmann Müller Foundation (grant: 1912) and the Olga Mayenfisch Foundation. Finally, we thank all the participating children and their families.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2019.100717>.

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