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## The rise and fall of rapid occipito-temporal sensitivity to letters: Transient specialization through elementary school

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### ABSTRACT

Letters, foundational units of alphabetic writing systems, are quintessential to human culture. The ability to read, indispensable to perform in today's society, necessitates a reorganization of visual cortex for fast letter recognition, but the developmental course of this process has not yet been characterized. Here, we show the emergence of visual sensitivity to letters across five electroencephalography measurements from kindergarten and throughout elementary school and relate this development to emerging reading skills. We examined the visual N1, the electrophysiological correlate of ventral occipito-temporal cortex activation in 65 children at varying familial risk for dyslexia. N1 letter sensitivity emerged in first grade, when letter sound knowledge gains were most pronounced and decayed shortly after when letter knowledge is consolidated, showing an inverted U-shaped development. This trajectory can be interpreted within an interactive framework that underscores the influence of top-down predictions. While the N1 amplitudes to letters correlated with letter sound knowledge at the beginning of learning, no association between the early N1 letter response and later reading skills was found. In summary, the current findings provide an important reference point for our neuroscientific understanding of learning trajectories and the process of visual specialization during skill learning.

### 1. Introduction

Letters are the foundation of alphabetic languages. When learning how to read, we start by linking letters with their corresponding speech sounds. This learning process necessitates a reorganization of the visual systems evolved for shape processing to facilitate letter processing (Altarelli et al., 2014; van Atteveldt and Ansari, 2014). Visual specialization for fast recognition of letters is key for attaining automaticity in reading alphabetic orthographies (McCandliss et al., 2003; Houdé et al., 2010). The term *visual specialization* is used here to describe changes in sensitivity to print in cortical networks that parallel the development of reading skills. The term *sensitivity* instead refers to brain responses that are stronger for print (single characters or letter strings) as compared to visually matched false font characters, consistent with our previous work (e.g., Brem et al., 2010, 2018; Pleisch et al., 2019a). As a result of

increasing visual specialization, some areas of the visual system are integrated to the complex language and reading network (Vogel et al., 2013) that grants the expert reader fast and direct access to semantic information, i.e., sight word reading (Ehri, 2017).

There is consistent evidence showing that an early failure to efficiently 'tune' visual areas to print might be involved in reading impairments, such as those in individuals diagnosed with dyslexia (see review and meta-analysis in Richlan et al., 2011; Norton et al., 2015). Developmental dyslexia is a specific reading disorder with a neurobiological and hereditary component, affecting 3–10 % of children (Snowling, 2013). Paradoxically, diagnosis usually takes place after reading failure in second grade or later, but targeted interventions seem to be more effective if applied in earlier stages, which motivates the investigation of reading precursors (Ozernov-Palchik and Gaab, 2016). In individuals of affected families, prevalence rates of dyslexia increase

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to 30–65 % (Pennington and Lefly, 2001). Children with familial risk for dyslexia form thus a group of special interest for neuroscientific studies of reading, reading acquisition and prevention. With longitudinal data across the course of elementary school this study aimed to clarify how learning to read changes visual sensitivity to letters. Insights into the developmental trajectories of visual specialization in occipito-temporal areas are particularly interesting because such measures may serve as potential early markers of reading skills and risk for dyslexia.

A brain region within the left ventral occipitotemporal cortex (vOTC) that includes the midfusiform gyrus has been termed as the visual word form system since it shows preferential activation to printed words compared to non-orthographic symbols (McCandliss et al., 2003; Centanni et al., 2018). Functional magnetic resonance imaging (fMRI) studies showed a pattern of preferential vOTC activation along a posterior-anterior gradient for increasingly wordlike stimuli (Vinckier et al., 2007; van der Mark et al., 2009) and that is sensitive to extensive experience with a specific orthography (Baker et al., 2007). In this context, some authors also described a ‘visual letter form area’ involved in processing of letters posterior to the centre of the word form system (Tagamets et al., 2000; James et al., 2005; Thesen et al., 2012). A recent study provides a more detailed description of vOTC function (Lerma-Usabiaga et al., 2018). By using functional, structural and quantitative MRI analyses, two functionally segregated regions within the most posterior and medial/anterior portions of the vOTC involved in perceptual and lexical stimulus contrasts were described, respectively. These findings support the notion of a visual word form system comprised of areas for bottom-up processing of perceptual information, along with other areas to integrate both bottom-up and top-down information. The latter would act as a hub for other systems of the language network and constitute the more ‘classically’ defined visual word form area (Vogel et al., 2012; Glezer and Riesenhuber, 2013; Nestor et al., 2013).

An unresolved issue is how vOTC specialization is shaped by reading instruction and practice. Developmental data suggests an inverted U-shape trajectory of visual responses discriminating between words and symbols (Maurer et al., 2006). That is, beginning readers show maximal preferential vOTC activations for orthographic stimuli compared to pre-readers and expert readers. A similar developmental pattern was also found in a longitudinal fMRI study following ten children from preschool to primary school in 6–7 MRI sessions (Dehaene-Lambertz et al., 2018). The study found that preferential activation to words in the visual word form area emerged in vOTC and peaked at the onset of school, followed by a slight decline afterwards. This area was stable over time and did not emerge at expense of recruiting areas with initially strong specialization to process faces. Instead, words ‘invaded’ visual areas that were weakly specialized in pre-reading stages. Some studies also describe an earlier, coarse vOTC sensitivity to orthographic stimuli (Brem et al., 2010; Eberhard-Moscicka et al., 2015) and a protracted development for finer contrasts (Centanni et al., 2017).

The observed trajectory of vOTC activations has motivated an interactive account of visual specialization (Price and Devlin, 2011). This view emphasizes the influence of top-down signals from other areas placing the vOTC system within a predictive coding framework (Friston, 2010). In short, this theoretical framework suggests a tendency to minimize prediction error, i.e., the differences between sensory input and prediction signals (Friston, 2010). Thus, the interactive account of vOTC specialization uses predictive coding to suggest that the strongest activations would concur with initial learning, driven by emerging prediction inputs combined with high prediction error (Price and Devlin, 2011). Subsequently, activation levels would decrease due to a progressive reduction in prediction error signal with growing experience. So far the evidence for the course of specialization is still fragmented and mostly based on whole word processing (Maurer and McCandliss, 2008). It is expected that letter processing, like any other learned visual category would also operate under this optimization mechanism, receiving top-down predictive signals from hierarchically

higher areas. Of note, top-down contributions may not be limited to semantic or phonological regions but also involve basic perceptual and attentional processes, since the vOTC is also strongly connected to the dorsal fronto-parietal attention circuitry (Chen et al., 2019). Here, we investigate vOTC responses to letters at five time points from preschool and over a key period for learning, in the first years of elementary school. Importantly, single letter processing targets a form of visual specialization less influenced by some aspects of word form processing such as semantic predictions.

Our focus is on the main electrophysiological correlate of vOTC activity. The visual N1 response is an early component of the event-related potential (ERP) that peaks around 200 ms after stimulus presentation. For print, it shows a posterior and bilateral or left-lateralized occipito-temporal topography (Maurer et al., 2011; Fraga González et al., 2014) and its sources correspond to the visual word form system in the vOTC (Rossion et al., 2003; Brem et al., 2009). N1 amplitudes reflect general expertise to visual stimuli (Tanaka and Curran, 2001; Gauthier et al., 2003). More relevant to the present study, the N1 amplitude is also sensitive to the word-likeness of visual stimuli and has been associated to individual differences in reading ability and dyslexia (Maurer et al., 2008; Brem et al., 2013; Hasko et al., 2013; Fraga González et al., 2014, 2016). Consequently, the N1 is a strong candidate in the search for a marker of print specialization and early identification of reading impairments. Moreover, the N1 has recently shown a reponse pattern supporting the predictive coding framework in that the N1 to Chinese characters with low visual-orthographic regularity was stronger in children with poor lexical classification skills, but lower in children with high lexical performance (Zhao et al., 2019).

Here, we examine the N1 responses to single letter vs false font to characterize early visual sensitivity to print. Single letters contain minimal semantic information, but they become strongly associated with speech sounds already in the first years of schooling. Because of this, N1 responses to letters (henceforth letter-N1) can be an important early indicator of dysfunction that is independent of general language and comprehension skills. A series of previous studies on children in third grade, found that N1 amplitudes to words discriminated between dyslexics and typical readers (Fraga González et al., 2014) and were associated with gains after a reading training (Fraga González et al., 2016). Moreover, the word-N1 changes with training also correlated with an audiovisual integration component measured in a passive oddball paradigm (Fraga González et al., 2017), supporting a relation between the quality of letter-speech sound integration and visual specialization (Blomert, 2011). A recent report examined vOTC sensitivity to words in elementary school children with a family history of dyslexia but heterogeneous risk and reading ability levels (Pleisch et al., 2019b). The results suggested subtle differences between poor and typical readers and large individual variability in the level of vOTC word sensitivity. Finally, a longitudinal assessment of letter string processing with a fast visual periodic stimulation paradigm showed an increase in left hemispheric letter-selective responses from first to second grade (van de Walle de Ghelcke et al., 2020), also suggesting rapid neural specialization with emerging reading skills.

The main goal of the present study is to characterize the process of visual specialization to single letters in a longitudinal approach covering five years of the most critical phase of learning to read in children. Based on previous ERP findings on the N1 for words and the interactive account of vOTC function, we test whether the letter-sensitive N1 follows an inverted U trajectory. We hypothesize that letter-sensitivity will show the strongest effects at the developmental stage when learning letter-speech sound associations is most pronounced. In addition, we examine how the N1 response to letters and letter sensitivity is related to individual differences in reading ability and familial risk and whether these N1 responses are related to children’s later reading outcomes.

**Table 1**  
Sample characteristics.

	<i>M (SD)[min,max]</i>
N	65
Sex ratio (male:female)	29:36
Handedness (right:left:both) <sup>a</sup>	53:8:1
Nonverbal IQ (HAWIK-IV at T1) <sup>b</sup>	105.66 (13.81) [80, 140]
Nonverbal IQ (RIAS at T6) <sup>c</sup>	102.78 (7.4) [88, 121]
ARHQ <sup>a,d</sup>	0.48 (0.16) [0.15, 0.80]

<sup>a</sup> N = 62; <sup>b</sup> N = 38; <sup>c</sup> N = 46; <sup>d</sup> The familial risk level was low in 7 children (10.77 %, ARHQ < 0.3), moderate in 15 children (23.08 %, ARHQ range 0.3–0.4) and high in 43 children (66.15 %, ARHQ > 0.4).

## 2. Materials and methods

### 2.1. Participants and group assignments

The current sample is part of a group of German-speaking children who participated in a large longitudinal study with simultaneous EEG/fMRI sessions, behavioral tests and a grapheme-phoneme based reading training (Mehringer et al., 2020). Here, we focus on data from kindergarten (T1), middle of first grade (T2), end of first grade (T3), middle of second grade (T4), and middle of fifth grade (T5) of elementary school. Only data from participants meeting our stringent EEG data quality criteria in at least one time point were analyzed (see section 2.5). In total, 65 participants fulfilled these criteria (36 female; age range 6.09–12.12, see Table 2 for age at each time point). Demographic information of this sample is presented in Table 1. The number of participants available for each time point were 31, 35, 35, 32 and 42, for T1, T2, T3, T4 and T5, respectively (see data overview on Fig. A.1). Children's familial risk for developmental dyslexia was estimated by assessing the reading history of the parents using the Adult Reading History Questionnaire (ARHQ; Lefly and Pennington, 2000). Individual risk scores were defined as the highest parental ARHQ value (see Table 1). All participants had nonverbal IQ scores > 80, normal or corrected to normal visual acuity and no neurological or cognitive impairments. One participant had a diagnosis of ADHD (medication was interrupted 48 h before test sessions), two participants reported having one sibling with reading impairments and one participant presented

**Table 2**  
Descriptive statistics showing reading scores at each time point.

	T1 (N = 31) M (SD)	T2 (N = 35) M (SD)	T3 (N = 35) M (SD)	T4 (N = 32) M (SD)	T5 (N = 42) M (SD)
Age	6.66 (0.30)	7.33 (0.29)	7.63 (0.29)	8.34 (0.31)	11.40 (0.41)
Letter knowledge <sup>a</sup>					
Sounds	15.71 (10.26)	44.66 (5.84)	47.60 (2.94)	49.48 (2.82)	–
Rapid automatized naming					
Letters	–	1.03 (0.34)	1.27 (0.40)	1.41 (0.38)	2.07 (0.51)
Numbers	–	1.03 (0.28)	1.13 (0.33)	1.36 (0.37)	1.98 (0.52)
Objects	0.61 (0.12)	0.68 (0.14)	0.74 (0.18)	0.86 (0.18)	1.13 (0.21)
Colors	0.57 (0.16)	0.68 (0.26)	0.70 (0.23) <sup>f</sup>	0.80 (0.27)	1.00 (0.22)
Phonological processing					
TEPHOBE					
Rhyme	4.94 (1.31)	5.09 (1.40)	5.26 (1.09)	–	–
Initial sound categorization	3.06 (1.75)	5.46 (1.84)	6.14 (1.12)	–	–
BAKO					
Phoneme deletion	0.55 (1.41)	2.94 (2.09)	3.03 (2.16)	–	–
Pseudoword segmentation	0.81 (1.42)	3.57 (1.80)	4.29 (1.58)	–	–
Vowel substitution	1.03 (1.78)	5.40 (2.37)	6.06 (1.71)	6.56 (1.48)	–
SLRT-II reading					
Word	–	8.09 (5.94)	14.37 (9.45)	28.00 (12.33)	63.95 (24.13)
Pseudoword	–	11.91(7.48)	15.71 (7.45)	21.81 (6.78)	39.98 (16.21)
Word (PR)	–	–	49.84 (27.31)	30.44 (22.77)	31.82 (28.79)
Pseudoword (PR)	–	–	44.37 (25.81)	27.61 (19.47)	34.07 (31.54)
Average (PR) <sup>d</sup>	–	–	47.11 (25.02)	29.02 (20.09)	32.95 (29.61)

<sup>a</sup> Sum of scores for items in lower and upper case (max score = 52). <sup>b</sup> 4 missing cases (N = 31); <sup>c</sup> 1 missing case (N = 34); PR = percentile score. Raw scores are: number of correct items (Letter knowledge, TEPHOBE, BAKO), number of correct items per second (rapid automatized naming) and number of correct items within 1 min (SLRT-II). <sup>d</sup> Average percentile of word and pseudoword reading fluency used for group assignment.

with delayed speech development. All children gave oral assent and parents gave written informed consent. The children received vouchers and presents as compensation for their participation. The project was approved by the local ethics committee of the Canton of Zurich and neighboring Cantons in Switzerland.

For the group comparisons, the sample was split based on the average of the individual percentile scores for word and pseudoword reading (see section 2.2). Participants were classified as poor readers if their average reading score at T5 was below the 16<sup>th</sup> percentile. If T5 scores were not available, we used scores at T4 (n = 17). The means (SD; range) of the average reading scores for poor (n = 24) and typical readers (n = 38) were 6.40 (4.39; 1–14.75) and 51.24 (21.66; 17.50–96), respectively. See Appendix B, Table B.1 for group scores in other tests.

### 2.2. Cognitive assessments

Participants performed a series of cognitive tests at each time point (Table 2). Only tests relevant for each stage of schooling were assessed. A more detailed description of these tests is presented in the Appendix A section 1.2. Letter knowledge was assessed from T1 to T4 by asking participants to first pronounce the (German) speech sound of each letter from the Latin alphabet presented in blocks of upper and lower case letters (52 items in total). Participants were also asked to name these letters, but this was, as expected, more challenging for children in the early time points (see Appendix B). In addition, we assessed rapid automatized naming (RAN) with subtests letters, numbers, colors and objects, and the phonological skills with subtests rhyme and initial sound categorization of the "Test zur Erfassung der phonologischen Bewusstheit und der Benennungsgeschwindigkeit" (TEPHOBE; Mayer, 2011) and subtests of the "Basiskompetenzen für Lese-Rechtschreibleistungen" (BAKO; Stock et al., 2013) test batteries. Reading fluency was measured with the two 1-minute reading tests (word reading, pseudoword reading) of the "Salzburger Lese- und Rechtschreibtest" (SLRT-II; Moll and Landerl, 2010). Average percentile scores of word and pseudoword reading for the later time points (T4 or T5 when available) were used to classify participants as poor or typical readers (see section 2.1). Finally, nonverbal IQ was estimated at T1 with the block design test of the Wechsler Intelligence Scale for Children

(HAWIK-IV; Petermann and Petermann, 2010) and at T5 with the Reynolds Intellectual Assessment Scales (RIAS; Reynolds and Kamphaus, 2003). No IQ scores were available for 8 participants.

### 2.3. Target detection task and stimuli

The current analysis focuses on an implicit audiovisual target detection task performed during the neuroimaging recordings. The complete paradigm was divided in three (at T5) or four parts (at T1-T4) of 375 s, each of them presenting unimodal visual and auditory, as well as bimodal stimulation blocks separated by fixation periods of 6 or 12 s. Each time point included the presentation of the following three character types: letters, digits, and false fonts. Participants were instructed to press a button whenever a target stimulus (picture or sound of an animal/tool) appeared on the screen. The task is illustrated in Appendix A, Fig. A.2. The present analyses focus on the processing of two unimodal visual conditions: letters (LET) and false fonts (FF) each consisting of 4 blocks with 15 items per condition (in total 54 trials + 6 target trials per condition). In the LET condition the stimuli included the letters *b, d, m, t, u, z* from the Latin alphabet presented in 'Swiss school' font (Appendix A, Fig. A.2.). In the FF condition the stimuli were one of two sets of characters counterbalanced across subjects and matched in size and width with the LET characters, created by rearranging different parts of those letters (Karipidis et al., 2017; Pleisch et al., 2019a). All stimuli were visually presented using goggles (VisuaStimDigital, Resonance Technology, Northridge, CA) in the middle of a grey background (mean visual angles horizontally/vertically FF: 2.8°/4.8°; LET: 2.8°/4.8°). The stimuli in each block were presented pseudorandomized, with a duration of 613 ms and followed by an interestimulus interval of either 331 or 695 ms. The task was programmed and presented using Presentation® software (version 16.4, www.neurobs.com) and the design was adjusted to find a compromise between the optimal designs for EEG and fMRI recordings, and to account for the attentional demands of young children.

### 2.4. EEG data acquisition and preprocessing

EEG data were recorded using an MR-compatible 128-channel EEG system (Net Amps 400, EGI HydroCelGeodesic Sensor Net) during functional magnetic resonance imaging (fMRI) in a Philips Achieva 3 T scanner (Philips Medical Systems, Best, The Netherlands). The recording sampling rate was 1 KHz (DC-filter). Two additional electrodes registered the electrocardiogram (ECG). Impedances of the 128 scalp electrodes were kept below 50 kΩ and the EEG system was synchronized with the scanner clock to reduce gradient residual artifacts during the simultaneous EEG/fMRI recordings. The recording reference was located at Cz and the ground electrode (COM) was located posterior to Cz. Vibrations were minimized by covering the electrodes with a bandage retainer net and turning off the helium pump of the MRI scanner during image acquisition.

Data preprocessing was conducted using VisionAnalyzer 2.1 (BrainProducts GmbH, Munich, Germany). Simultaneous EEG-fMRI recordings induce a series of specific artefacts related to the MRI environment. This makes several additional artefact correction steps during preprocessing necessary as compared with conventional EEG recordings to attain high quality ERPs. Electrodes with overall poor data quality or excessive artefacts were topographically interpolated. MR artefacts were removed using the average template subtraction method (Allen et al., 2000) and ballistocardiogram artefacts were corrected using sliding average template subtraction as implemented in VisionAnalyzer 2.1. Additionally, continuous data were visually inspected to exclude periods with large artefacts like head movements. Subsequently, a band-pass filter of 0.1–30 Hz and 50 Hz Notch filter were applied and data were downsampled to 500 Hz. Then, we ran an independent component analysis (ICA) to remove components associated with blinks, eye movements, and residual ballistocardiogram artefacts. The mean (SD;

range) number of ICs rejected were at T1: 18.90 (1.42; 15–20), T2: 7.06 (2.46; 3–13), T3: 12.51 (3.55; 5–18), T4: 9.38 (4.02; 2–18), T5: 10.43 (4.01; 5–20). After artifact correction, data was visually inspected, electrodes located on the cheeks (E43, E48, E119, E120) were removed as their signal was often contaminated by major artifacts and a 0.1 Hz high-pass filter was applied to minimize residual slow artifacts. Finally, data were re-referenced to the common average reference.

### 2.5. Event-related potential analysis

The continuous EEG data were epoched from -100 to 613 ms after stimulus onset. Epochs with amplitudes  $\pm 200$   $\mu\text{V}$  or visually identified as containing residual artifacts were discarded from analysis. Only participants with at least 20 epochs in each condition were included in the analysis. The mean (SD) number of epochs for the LET condition were T1: 43.16 (8.32), T2: 42.23 (8.86), T3: 46.09 (7.18), T4: 42.03 (9.17) and T5: 47.50 (5.54). For the FF condition they were T1: 40.61 (8.86), T2: 42.14 (8.56), T3: 45.97 (5.92), T4: 40.72 (10.98) and T5: 47.71 (5.11). There was no evidence for significant differences between conditions in the number of epochs in any of the time points,  $p_s > 0.142$ . The N1 interval was defined using the global field power (GFP; Lehmann and Skrandies, 1980) of the ERP averaged across both conditions and all subjects. The GFP quantifies the activity at each time point taking into account activity of all electrodes simultaneously. Thus the peaks in GFP plotted over time can be used to determine the latencies of evoked responses and those peaks are often assumed to reflect time periods of maximal processing in the brain. The N1 interval was defined as  $\pm 30$  ms around the second GFP peak after confirming that latency and the topography of activity of that interval corresponded with the expected N1 characteristics. This was defined independently at each time point to account for potential latency differences between measurements: T1: 198–258 ms, T2: 198–258 ms, T3: 194–254 ms, T4: 188–248 ms and T5: 180–240 ms (see Appendix B, Fig. B.1 for topographical maps of activity in P1 and P2 intervals). Lastly, mean amplitudes of the N1 intervals were computed from the signal of the left occipitotemporal cluster (LOT): E57, E58(=T5), E65, E70(=O1), E63, E64, E69, E68, E73 and the right occipitotemporal cluster (ROT): E83 (=O2), E90, E96(=T6), E100, E89, E95, E99, E88, E94. The clusters were defined based on visual inspection of topographies and previous studies (Pleisch et al., 2019a).

### 2.6. Statistical analysis

The main analysis of the N1 letter sensitivity development included a linear mixed model (LMM) with a random intercept on N1 mean amplitudes and the fixed factors hemisphere (LOT, ROT), condition (letter, false font) and time point (T1, T2, T3, T4, T5). The model was implemented with the function *lme* of the R package 'Nlme' (Pinheiro et al., 2019). The LMM approach can handle missing values, which allowed us to use all data in the analysis including participants for whom only data from one time point was available (see sample overview in Appendix A, Fig.A.1). In our models, outliers were excluded if the normalized residuals exceeded the  $\pm 3$  threshold, which resulted in exclusion of 8 data points (1.14 % of the data) in the main model (note that Figs. 3 and 4 presents all values irrespective of model-wise exclusions). Q-Q plots and predicted vs residual plots were inspected to assess whether the data met the assumptions of normality and homoscedasticity.

Subsequently, we followed up the N1 sensitivity to letters with post-hoc *t*-tests. Tukey Kramer correction was applied to *p* values in the post-hoc comparisons. Further LMMs for each time point are described in the supplemental material (Appendix B, Table B.3). In addition, t-maps show the topography of the differences between letters and false fonts across the N1 interval. For the group comparisons, we used the same LMM approach including the factor group (poor and typical readers) as in the main model and two separate LMM models for each group separately. The group sizes per time point (T1 to T5) for typical readers were 20, 19, 18, 20 and 25; for poor readers they were 8, 14, 15, 12 and 17,

respectively. Letter sensitivity effects again have been followed up with post-hoc *t*-tests and time point wise LMMs are presented in the supplemental material (Appendix B, Table B.4). Furthermore, we examined differences in topography between conditions during the N1 period with a topographical analysis of variance (TANOVA; Strik et al., 1998) at each time point. Normalization per case was done to examine differences that are irrespective of voltage amplitudes, thus indicating topographical changes related to differences in source configurations rather than just signal strength. In this approach, bootstrapping (5000 permutations) statistics were computed per data point resulting in a set of *p* values that indicate significance levels of map differences between conditions. TANOVA was implemented using in-house scripts with Matlab functions (R2017a, MathWorks, Natick, MA). Finally, we used linear regression to study the association between neural measures (N1 responses to letters, the difference between N1 amplitudes to letters and false fonts) and behavioral measures of interest (letter knowledge and reading).

## 2.7. Data availability

Further information and requests for resources should be directed and will be fulfilled by the Lead Contact, Silvia Brem ([sbrem@kjpgd.uzh.ch](mailto:sbrem@kjpgd.uzh.ch)). Some restrictions apply for data sharing for ethical reasons, to protect participant confidentiality and privacy.

## 3. Results

### 3.1. Cognitive performance

The analysis of cognitive tests assessing letter knowledge, word and pseudoword reading, phonological processing and rapid automatized naming, yielded time point effects suggesting improvements in all the main assessments (see sample demographics in Table 1 and descriptive statistics of cognitive assessments in Table 2). More relevant to our N1 analysis, letter knowledge strongly increased from T1 to T2, and reached ceiling levels at T3 and T4 (therefore letter knowledge was not assessed at T5). These results are illustrated in Fig. 1. A detailed statistical report of these results and further cognitive assessments is provided in Appendix B.

### 3.2. ERP analysis

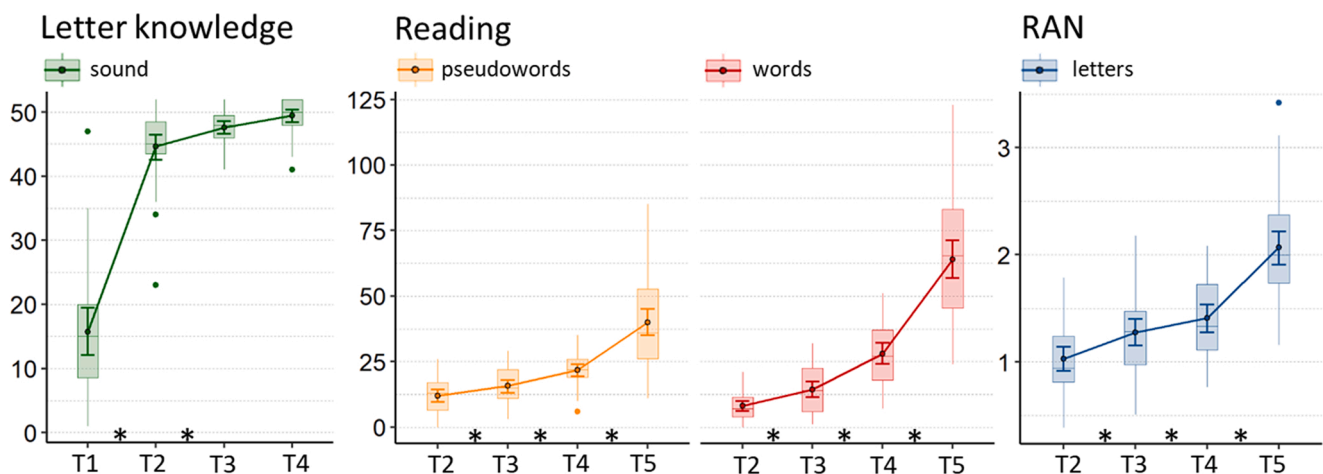
The visual N1 mean amplitude to the experimental conditions of letters and false fonts in the target detection task was used for statistical

analyses.

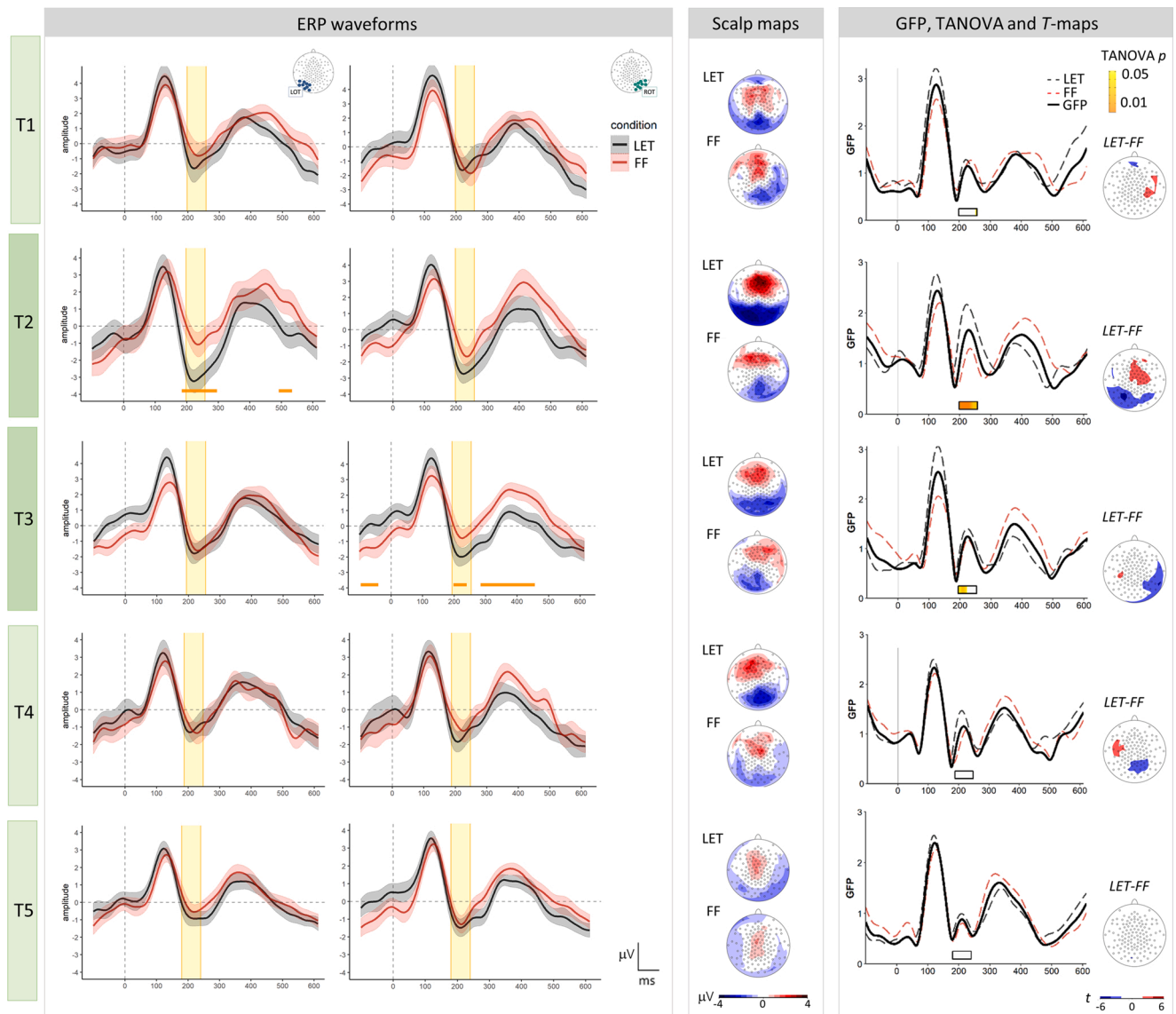
#### 3.2.1. Development of N1 sensitivity

**3.2.1.1. N1 mean amplitude.** The ERPs for each time point (T1 to T5) and condition for the left and right occipito-temporal electrode clusters (LOT and ROT respectively) are shown in Fig. 2. We performed a linear mixed model (LMM) analysis on N1 mean amplitudes to examine the effects of the factors time point, condition and hemisphere (see sections 2.5 and 2.6 for details about models and the selection of the N1 interval). The analysis revealed a main effect of time point ( $F(1,4) = 5.53, p < 0.001$ ) indicating significant differences over time. Moreover, there was a main effect of condition, ( $F(1,608) = 29.20, p < 0.001$ ), indicating stronger amplitudes for letters vs false fonts and an interaction with time point ( $F(4, 608) = 2.87, p = 0.022$ ) showing differences in letter sensitivity across time points. In addition, there was a trend for a main effect of hemisphere, ( $F(1,608) = 3.19, p = 0.074$ ), suggesting slightly larger amplitudes in the right vs left clusters across time points and conditions. No other effects were statistically significant,  $ps > 0.286$  (see further statistical information in Appendix B, table B.3 and figure B.3).

The interaction between time point and condition was followed by post hoc *t*-tests. The tests revealed that letter sensitivity was significant at T2 and T3,  $t(608) = -5.16, p < 0.001$  and  $t(608) = -2.79, p = 0.005$ , respectively. There was a trend for a condition effect at T1,  $t(608) = -1.83, p = 0.067$ , but not for the later time points,  $ps > 0.170$ . The mean amplitudes per condition for each time point can be seen in Fig. 3 (see Appendix B, Table B.2 for descriptive statistics). We found no statistical support for differences between hemispheres in letter sensitivity at T2 or T3. However, the ERP waves with CIs at T2 and *t* maps (Fig. 2) suggest that the effect of condition may be more robust for LOT vs ROT clusters. The additional *t*-tests per data point of the waveforms ( $ps$  below 0.05 are displayed in the color map in Fig. 2) comparing conditions showed significance (false discovery rate-corrected) in the N1 interval only for the LOT at T2 and the ROT at T3. In addition, we also inspected the topographical distribution of the letter-false font difference in Fig. 2 (right panel). The topographies of the *t*-tests for the difference between conditions show a left distribution for the strongest *t* values at T2, suggesting that this difference is more consistent across electrodes in the left hemisphere. At T3 only a region of significant *t* values appears over the right hemisphere. Inspection of individual variability also informs us about potential differences between left and right electrode clusters. The individual values of the N1 letter-false font mean amplitudes can be seen in Fig. 4. Values below zero in that figure indicate stronger negative



**Fig. 1.** Cognitive performance across measurements. Y-axis in the letter knowledge (green) panel indicates the number of correctly pronounced letter sounds (upper and lower case items summed); in reading, the number of correctly read pseudowords (orange) and words (red) within a minute; in RAN letters (blue) the score is the number of letters named per second. Error bars indicate mean and 95% CIs. Asterisks in x-axis indicate significant differences between pairs of measurements ( $p < 0.05$ ). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 2.** EEG results per time point (T1 to T5). Left panel: ERPs ( $\mu\text{V}$ ) for letters (black lines) and false fonts (red lines) with ribbons indicating 95 % CIs (within-subject). The N1 interval is highlighted in yellow and the horizontal orange bars show  $p < 0.05$  in  $t$ -tests per data point (FDR corrected). Middle panel: scalp topographical maps for letters and false fonts ( $\mu\text{V}$ ). Right panel: GFP for both conditions (black lines) and false fonts (dashed red lines) in  $\mu\text{V}$ . Box near the x-axis shows TANOVA results for the N1 interval (yellow-orange gradient shows  $p_s < 0.05$  in permutation tests). Scalp maps in the right show the  $t$  values as  $t$ -test maps for the difference between letters and false fonts. ERPs = event-related potentials; CIs = confidence intervals; FDR = false discovery rate; GFP = global field power; TANOVA = topographic analysis of variance; LET = letters; FF = false fonts; 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.)

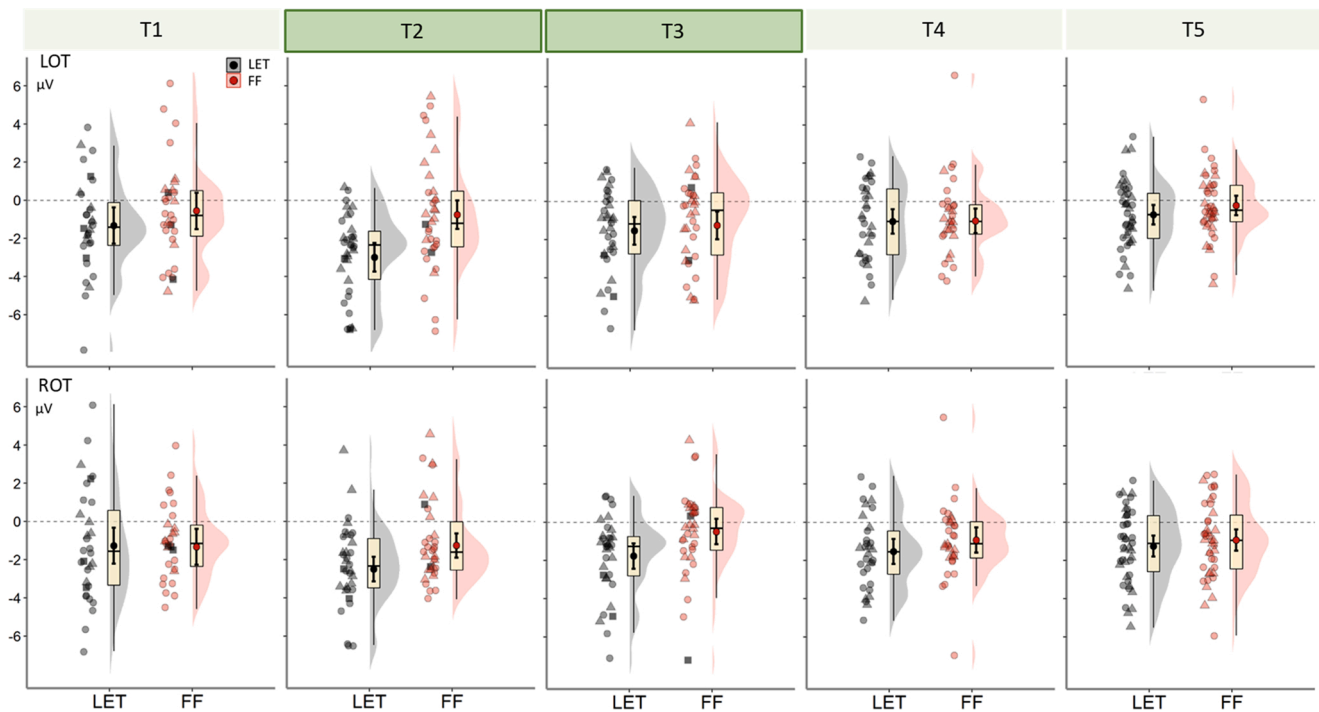
amplitudes for letters compared to false fonts. At T2, N1 amplitudes to letters were stronger than to false fonts in 74.29 % of the children for LOT and in 65.71 % for ROT. At T3, this was the case for 54.29 % of the children for LOT and 65.71 % for ROT. For the other time points, i.e., T1, T4 and T5, these percentages ranged from 53.12–62.50 %. The distance from zero of the upper boundaries of the 95 % CIs for the left cluster at T2 relative to the right cluster at T2 and T3 also suggests a stronger condition effect at T2 in the left cluster (Fig. 4).

To sum up, our main analysis revealed an inverted U-shaped developmental pattern of letter sensitive processing during reading acquisition as indicated by the absence of condition differences at T1, T4 and T5 and pronounced letter-sensitivity at T2 and T3. Additional inspection of the topographical distribution of condition difference reflecting letter sensitivity suggest that at T2 this effect may be more consistent across electrodes in the left hemisphere. In addition, inspection of individual variability shows that the pattern of stronger amplitudes for letters vs

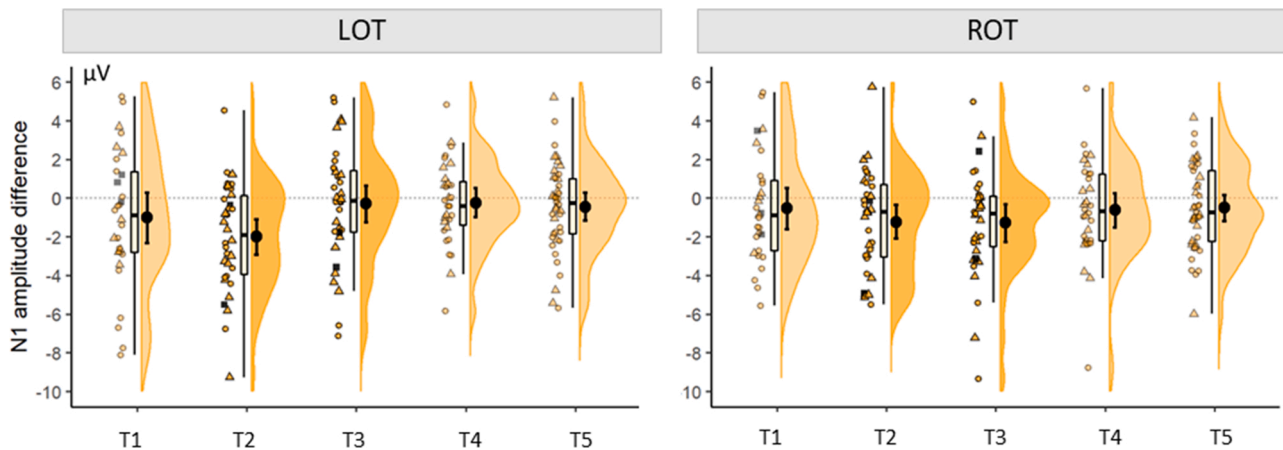
false fonts is present in more participants in the left cluster and at T2.

**3.2.1.2. Topographic analysis of variance (TANOVA).** As a supplement to our main analysis, the topographical distribution of activations for letters and false fonts were compared at each time point for the N1 interval (see topographies in Fig. 2, middle panel). At T2 the TANOVA results suggest statistically significant differences in topographies between letters and false fonts across most of the N1 interval (see box in Fig. 2 in right panel). Since normalized activation maps were used in this analysis, the topography differences are considered independent from intensity. The analysis also yielded map differences at T3 although only in the initial portion of the N1 interval. No significant map differences in the N1 interval were found at T1, T4 and T5.

**3.2.2. Associations between N1 amplitude, reading level and familial risk**  
Previous studies linked atypical print processing as measured with



**Fig. 3.** N1 mean amplitudes ( $\mu\text{V}$ ) for letters (black) and false fonts (red) for left and right clusters (top and bottom row, respectively) per time point. Those time points with significant condition effects are highlighted in dark green. The shape of the scatter points indicates whether a participant was classified as typical (circle) or poor reader (triangle); square shapes indicate that the participant was not classified as no reading scores were available. Error bars within the density plots show the mean and 95 % CI. LOT = left occipito-temporal; ROT = right occipito-temporal; LET = letters; FF = false fonts. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



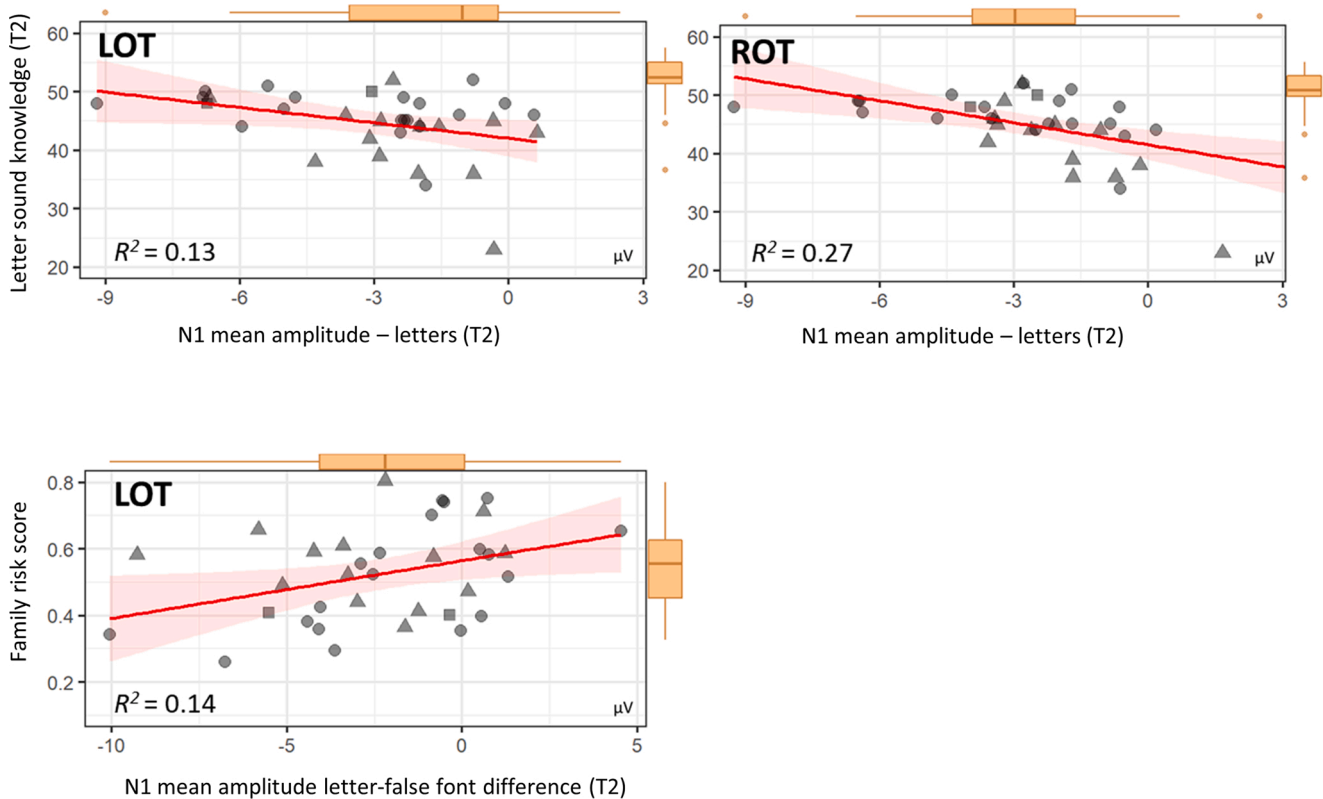
**Fig. 4.** Differences in N1 mean amplitudes between letters and false fonts per time point. The shape of the scatter points indicates whether a participant was classified as typical (circle) or poor reader (triangle); square shapes indicate that the participant was not classified as no reading scores were available. Error bars within the density plot show the mean and 95 % CIs. More negative values indicate stronger (negative) amplitudes for letters vs false fonts. LOT = left occipito-temporal; ROT = right occipito-temporal.

the N1 or vOTC activation to reading skills and familial risk (Bach et al., 2013; Brem et al., 2013; Karipidis et al., 2017, 2018). Therefore we examined in a second step the association between the N1 and readings skills as well as familial risk for dyslexia. The N1 variables of interest were the mean amplitudes in left and right electrode clusters. The mean N1 amplitudes to letter-false font differences were used as an index of letter sensitivity. N1 amplitudes to letters were also explored as a less specific measure of vOTC activation. N1 amplitudes at the first two time points, T1 and T2, were included as predictors in linear regression analyses, since we focused on early markers of reading skills. First, we examined associations between N1 amplitudes with later reading levels. We found no significant correlations between letter or letter-false font

N1 at T2 and the word or pseudoword reading fluency scores,  $ps > 0.162$  (this was not examined at T1 as no reading scores were tested then). There was also no evidence for a significant association between letter or letter-false font N1 amplitudes at T1 or T2 and the last reading scores available from T4 and T5 that were used to assess reading outcome,  $ps > 0.161$ .

Second, we examined the association between the N1 at T1 and T2 as predictors, and letter knowledge scores at these time points. We found a relation between knowledge of letter sounds and N1 amplitudes for letters at T2 in the left ( $R = 0.36$ ,  $R^2 = 0.13$ ,  $\beta = -0.88$ ,  $t = -2.18$ ,  $p = 0.036$ ,  $p_{FDR} = 0.288$ ) and right electrode cluster ( $R = 0.52$ ,  $R^2 = 0.27$ ,  $\beta = -1.26$ ,  $t = -3.50$ ,  $p = 0.001$ ,  $p_{FDR} = 0.024$ ). The result at the





**Fig. 5.** Top panels. Linear regression with letter sound knowledge at T2 as dependent variable and N1 amplitudes ( $\mu\text{V}$ ) for letters at T2 (left and right clusters) as predictor. Bottom panel. Linear regression with familial risk score as dependent variable and T2 letter-false font N1 amplitude differences ( $\mu\text{V}$ ) in the left cluster as predictor. The shape of the scatter points indicates whether a participant was classified as typical (circle) or poor reader (triangle); square shapes indicate that the participant was not classified as no reading scores were available. Box plots are displayed in the margins. LOT = left occipito-temporal; ROT = right occipito-temporal.

right cluster was significant after correction for False Discovery Rate (FDR; Benjamini and Hochberg, 1995; applied over 24 tests reflecting the 4 neural and 6 behavioral measures at a given time point). These results, plotted in Fig. 5, suggest stronger N1 amplitudes to letters in children with higher knowledge of letter sounds. However, there was no significant association between letter sensitivity (measured as letter-false font N1) and letter knowledge in T2,  $p_s > 0.304$ . Using T1 data, we found no statistical evidence for a relationship between N1 measures and letter knowledge,  $p_s < 0.128$ .

Finally, we investigated whether familial risk scores were associated with N1 responses. The analysis yielded a relationship between ARHQ scores and T2 letter-false font differences in N1 amplitudes in the left hemisphere (predictor) that was significant at an uncorrected  $p < 0.05$  threshold but not after FDR-correction,  $R = 0.37$ ,  $R^2 = 0.14$ ,  $\beta = 0.02$ ,  $t = 2.30$ ,  $p = 0.028$ ,  $p_{\text{FDR}} = 0.288$ . The result suggested more pronounced N1 letter-false font differences in children with lower risk scores. This relation is illustrated in Fig. 5 (bottom panel). No other significant association was found in the regression analyses with T1 or T2 data,  $p_s > 0.108$ .

### 3.2.3. N1 group differences between poor and typical readers

To examine whether poor readers exhibit a N1 development that diverges from typical readers (see details of group assignment in section 2.1), we repeated our main LMM analysis with the factors time point, condition, hemisphere, and the additional factor group (poor, typical readers). The analysis yielded a significant interaction between group and time point,  $F(4,567) = 3.79$ ,  $p = 0.005$  (see Fig. B.2), suggesting different trajectories of N1 amplitudes overall between the groups (these trajectories per group are plotted in Fig. B.3). Similar to previous analyses, the model also showed significant effects of time point,  $F$

(1,567) = 3.30,  $p = 0.011$ , and condition,  $F(1,567) = 23.49$ ,  $p < 0.001$ ; but there were no other significant interactions with group or main effect of group,  $p_s > 0.582$ . Based on the time  $\times$  group interaction we examined our main model in each group separately. The analysis with typical readers showed significant effects of time point,  $F(4,347) = 7.69$ ,  $p < 0.001$ , and condition,  $F(1,347) = 17.57$ ,  $p < 0.001$ , suggesting differences between time points but overall larger amplitudes for letters compared to false fonts across time points. No interactions were significant in this analysis,  $p_s > 0.207$ . In poor readers, likewise the main effect of condition was statistically significant  $F(1,220) = 8.62$ ,  $p = 0.004$ , but there was a trend for a time point  $\times$  condition interaction,  $F(1,220) = 2.13$ ,  $p = 0.078$ . More details about this tentative group analyses are provided in Appendix B section 2.3.4, table B.4 and figures B.3 and B.4 showing ERPs and development of mean amplitudes per group. In summary, the group-wise analyses suggest potential differences between typical and poor readers, however further examination in larger samples is required, due to the small sample of poor reading children (see section 2.6).

## 4. Discussion

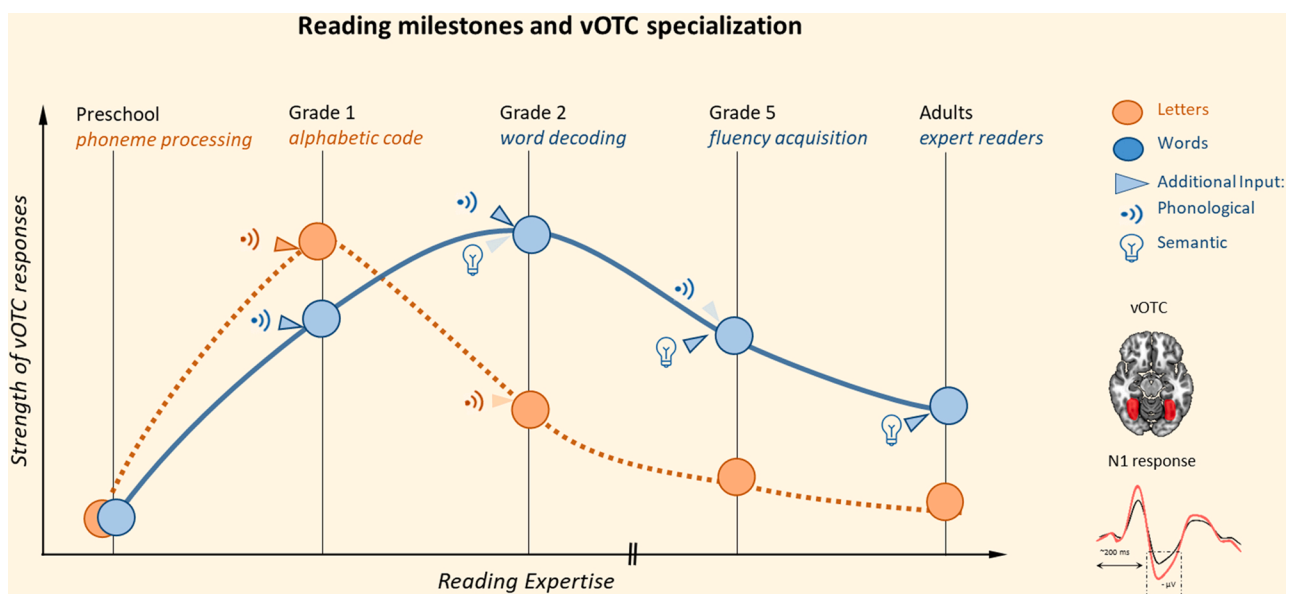
This study provides important novel insights into how learning to read influences the way the brain processes letters. Specifically, we clarify the course of vOTC specialization by examining N1 responses to single letters compared to false fonts in an implicit letter processing task during the critical period of reading acquisition. Our main analysis included one time point in prereaders, three measurements in beginning readers within the first 1.5 years of reading instruction, and a follow up measurement after several years of reading practice, towards the end of elementary school in fifth grade. We found evidence for emerging

bilateral N1 letter sensitivity in the middle and at the end of first grade (T2 and T3), a stage at school when substantial gains in letter knowledge are established and consolidated to enable reading. In addition, stronger responses to letters were associated with higher letter knowledge and higher letter sensitivity to lower familial risk for dyslexia. As anticipated, prereaders showed no signs of N1 letter sensitivity. Importantly, N1 letter sensitivity was no longer detected shortly after first grade, in the middle of second grade or later in fifth grade. Our findings support an inverted U-shaped developmental curve of visual sensitivity to single letters that peaks when children learn letter-speech sound correspondences at school.

The trajectory of letter-N1 sensitivity observed here has similarities to the development of the word-sensitive N1 (Maurer et al., 2011) and also converges with the rapid emergence of word sensitive processing in the vOT as revealed in fMRI studies (Brem et al., 2010; Saygin et al., 2016; Dehaene-Lambertz et al., 2018; Pleisch et al., 2019a). In the former ERP study, the N1 showed maximal word sensitivity in second grade, when fluent reading starts, and leveled off in fifth graders (Maurer et al., 2006, 2011). Several factors may have influenced those results, for instance, semantic access, decoding strategies or, as recently revealed, contextual facilitation (Heilbron et al., 2020). Here, we examined N1 tuning to single letters, which is largely unaffected by these factors. Altogether, the N1 'timelines' of letter processing and the studies on word processing suggest a strong engagement of the vOTC during initial learning that decays with advancing expertise. Based on this evidence, we illustrate the developmental course of words and letter vOTC responses in Fig. 6. Accordingly, strong responses to letters are restricted to the corresponding learning milestone, i.e., knowing the alphabetic code, and decay rapidly afterwards. Sensitivity to words starts in the same stage but peaks slightly after, with more effective word decoding, and is sustained for a longer period. Several contributors to these trajectories could be hypothesized along the lines of an interactive perspective based on predictive coding (Friston, 2010; Price and Devlin, 2011). First, prediction from phonological areas is expected to start earlier for single letters, taught and learned first, compared to words. Moreover, in most alphabetic languages a symbol presented individually

will be systematically associated with a sound (Ziegler and Goswami, 2005), but when embedded in a word, the phoneme associated with a letter may change depending on the orthographic transparency of the language. Thus, optimization of single character processing may also happen faster for single letters than for words. Words also present additional working memory and attentional demands of sequential grapheme-phoneme decoding, which is the prevalent strategy in beginning readers. The influence of phonological processing on the N1 is supported by a previous ERP study showing amplitude modulations by either an orthographical or phonological focus in the task (Yoncheva et al., 2010). Second, phonological demands in expert readers are expected to be progressively minimized while semantic access gains more influence in fast word recognition (Ehri, 2005). This growing semantic influence is not expected for single letters. In relation to this, the interactions between the vOTC and other sensory and higher association areas receives support from connectivity studies (Saygin et al., 2016; Stevens et al., 2017; Wang et al., 2020).

Our results support the model in Fig. 6 and suggest a fast rise and decay in letter sensitivity. This is an important addition to the current knowledge on reading development in the brain, which is mostly based on visual sensitivity at the word level. In particular, we identified a very narrow specialization window for the letter-sensitive N1 at the very beginning of reading acquisition, in the middle of first grade. Already towards the end of grade 1 (T3) letter sensitivity was detected in less participants than half a year earlier (T2; see Fig. 3). At this stage, most participants had already attained high proficiency in letter knowledge. Also, the regression analysis only showed an association of letter sound knowledge and the N1 amplitudes to letters at T2. An interpretation based on learning is supported by the association between knowledge of the letters' corresponding sounds and bilateral letter-N1 at T2. Current data, however, does not support an interpretation of this result in terms of neural sensitivity to letters, since the regression analysis was not significant for the letter sensitivity effect (letter-false font difference). Letter sound knowledge reflects the child's ability to produce the speech sound associated with a letter and performance at the end of first grade was already close to ceiling. The effects of learning letter-speech sound



**Fig. 6.** Schematic of a model for visual specialization, reflected in vOTC activity to letters (orange) and words (blue), with advancing reading expertise. Vertical lines represent learning milestones. Specialization to single letters is proposed to peak when letters are learned and decay afterwards, and specialization to words is proposed to peak later and then decline slower, persisting over time at more subtle levels. Arrow heads indicate the changing contributions from phonological and/or semantic areas. Phonological input would be stronger with initial learning and when grapheme-phoneme decoding is the main reading strategy. Semantic influence would be stronger with more advanced sight word reading strategies. Illustrations on the right margin show the location of the vOTC (red highlight) and the N1 response as the main electrophysiological correlate of its activity. vOTC; ventral occipital-temporal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associations on the vOTC activation to print have been previously reported in several training studies (Brem et al., 2010, 2018; Karipidis et al., 2017, 2018; Pleisch et al., 2019a; Taylor et al., 2019). The observed course of N1 letter sensitivity across measurements may also reflect differences in the allocation of attentional resources at T2, when children consolidate their knowledge of letter sounds. Attentional task demands and focus have been previously shown to have an impact on the N1 (Luck et al., 2000; Vogel and Luck, 2000; Yoncheva et al., 2010; Okumura et al., 2015). Further, a recent study reported that connections from the visual word form area to other language regions and to the dorsal fronto-parietal attention network, predicted language skills and visuo-spatial attention, respectively (Chen et al., 2019). The authors proposed a multiplex model of vOTC function, as a link between the language and attentional system, which is not incompatible with the interactive account (Price and Devlin, 2011). Ultimately, a comprehensive model of visual specialization for reading will need to integrate language, associative and attentional aspects involved in learning this complex skill.

An additional discussion point is the lateralization of the letter N1. Specialization in the vOTC to print has been typically reported to be left lateralized, as part of a left lateralized reading and language network. We found no significant effects of hemisphere on N1 responses to letters at T2, when the strongest sensitivity emerged. The inspection of the *t*-value maps for the letter-false font differences (Fig. 2) and inspection of the individual values (Fig. 3) suggested that letter sensitivity may be more consistent in the left hemisphere. Moreover, there was evidence for an association between N1 and letter knowledge for both left and right hemisphere clusters, but this association was stronger and remained significant after correction for multiple testing in the right hemisphere. These results may have been influenced by the topography of letter-N1 amplitudes, with a more posterior distribution than the typical word-N1 topography (e.g., Brem et al., 2013; Fraga González et al., 2014), consistent with the location of the putative letter-form area (Thesen et al., 2012). Further, the literature on lateralization of N1 to single-characters has been inconsistent, with reports of bilateral (Wong et al., 2005), right lateralized (Tarkiainen et al., 1999) and mixed lateralization (Stevens et al., 2013). The latter study found bilateral responses to single letters vs false fonts but also suggested a contribution of phonological processes in a rhyming task to N1 lateralization (Stevens et al., 2013). In view of current data and previous mixed findings, it seems that the lateralization of N1 to single characters remains ambiguous. This issue may need further examinations in future studies.

A further aim of this study was to clarify whether the N1 ERP to letters may serve as an index for the development of reading performance. Previous research pointed at the importance of letter-speech sound integration with regard to reading deficits in dyslexia (Blomert, 2011) and suggested learning and using novel sound-symbol associations as potential predictive measures of reading development (Horbach et al., 2015; Aravena et al., 2016, 2017). This view was however challenged by a recent behavioral study in typical beginning readers, where letter-sound knowledge but not automatic letter-speech sound priming predicted word reading skills (Clayton et al., 2020). The different approaches to measure symbol-sound integration may explain divergent findings on prediction of reading skills. Here we examine visual processing of letters, which undergoes fast and strong changes during the first months at school when children learn letter-speech sound associations. Even though the early visual N1 to single characters is influenced by learning grapheme-phoneme associations (Pleisch et al., 2019a), it is not known to what extent our implicit task captures letter-speech sound integration and/or automation processes. Previous studies showed that the N1 to words could complement the prediction of future reading skills (Bach et al., 2013; Brem et al., 2013). The current results, however, do not provide evidence for a significant association between the N1 to letters or the N1 letter-false font difference and later reading skills. A possible explanation is that the N1 response to single letters captures an early form of specialization with sources in the more posterior letter

form area within the vOTC (Thesen et al., 2012; Brem et al., 2020), which may not be equally sensitive to variations in reading skills. This is consistent with a previous finding showing an association of print sensitive activation and reading fluency only in the visual word form area but not in the posterior letter form area in school children (Brem et al., 2020).

The tentative results from the group comparison in the current study suggest overall differences in the development of the N1 amplitude over bilateral occipito-temporal scalp to characters (letters, false fonts) between groups (see figure B.4). Typical readers showed stronger inverted U-shaped amplitude development than their poor reading peers, but no differential letter sensitivity development. The current sample size provides first preliminary insights into potential differences, but reliable interpretation beyond the current sample would require validating these effects in larger samples. Future studies should clarify how letter sensitivity relates to successful reading acquisition and how it is associated to the development of the word-sensitive N1 response which has been shown to be related to reading outcomes in children (Bach et al., 2013; Brem et al., 2013; Fraga González et al., 2014). Finally, in relation to dyslexia risk indicators, the association between higher N1 letter sensitivity over the left scalp electrodes at T2 and lower familial risk supports previous findings of atypical neural responses in children with elevated hereditary risk (Debska et al., 2016; Karipidis et al., 2017; Nora et al., 2021), although its statistical significance is limited to uncorrected values. In particular, our result may also be compatible with previous findings of atypical audiovisual congruency effects (Karipidis et al., 2017) and underactivation (Debska et al., 2016) in occipitotemporal regions for children with heightened risk of dyslexia and with the more pronounced N1 response and ventral occipitotemporal activation reported to characters after character-speech sound training in those preschool children with better performance (Pleisch et al., 2019a).

#### 4.1. Limitations

The current sample consists of children with varying levels of risk for dyslexia and a third of all participants presented with low or moderate risk levels. This poses a limitation to the generalizability of the findings. Despite the limitations such samples may entail, studying them is important because children at-risk will particularly benefit from early interventions. Well-defined neurocognitive profiles associated with reading problems may in the future help to individualize support. An additional point of consideration is the EEG recording during fMRI scanning. Simultaneous recordings of EEG during fMRI have the advantage of providing novel insights into information processing with high temporal and high spatial resolution, at the expense of certain challenges to data quality. Extensive data preprocessing with different artefact removal steps is thus necessary along with stringent quality monitoring to achieve high quality ERPs. Similar to our previous studies in which we applied such combined measurements (Karipidis et al., 2018; Pleisch et al., 2019b), the current ERP waveforms and topographies do not suggest that this specific method has compromised the present analyses. Another point to be considered is the heterogeneity of the teaching methods used for reading acquisition at schools and the amount of additional support and intervention that children received during the study period. In the current study some children received support with a computerized grapheme-phoneme training (Mehring et al., 2020) at T2 or T3 or through special education teachers at school. Controlling for such factors is a major challenge in developmental studies on young children. Finally it needs to be stated that our current longitudinal sample is restricted in terms statistical power to examine complex models with three fixed factors and to compare the trajectories of different subgroups such as those based on familial risk or readings skills. This is a common limitation to longitudinal developmental studies in the field (see review in Chyl et al., 2021) which is especially difficult to overcome in neuroimaging studies. Here we provide some tentative analyses of longitudinal trajectories in groups of children with poor and

typical reading skills that should motivate more research on that topic in the future. Even though our data provide some insights into potential relations of familial risk and the strength of letter sensitivity and also differences in the visual N1 development in typical and poor reading children, such indications need further investigations and longitudinal studies in large samples to be confirmed.

#### 4.2. Conclusions

This study characterizes the rapid specialization of visual systems before, during and after letter sound learning, a pivotal period in reading acquisition. Our findings revealed a narrow time window for the emergence of distinctive N1 sensitivity to letters vs false fonts in the middle of first grade. These results support an inverted U course of visual specialization to print. Previous work suggested such a trajectory for visual word processing with N1 sensitivity peaking around 1–2 years after school enrolment in second grade (Maurer et al., 2006). Here, we demonstrate for the first time that this developmental pattern is also evident for single letters, but peaks earlier, in first grade, when knowledge of letter sounds is attained and declines fast after consolidation. We found evidence for a relationship between the strength of the electrophysiological brain responses to letters and letter knowledge in beginning readers. Group analyses based on reading skills suggested potential differences in early lateralization and sensitivity trajectories that would be of interest for further studies. It remains to be clarified how early visual specialization to letters relates to later visual specialization to words and reading outcomes. The narrow and critical time window of N1 sensitivity to letters characterized in this study is an important point of reference to guide future research aimed at studying brain changes during reading acquisition.

#### Author contributions

GFG; conducted data analysis, statistics and visualizations. GP, IK, SDP, JN; collected the data. GFG, GP, IK, SDP, JN; preprocessed the data. SW and SB provided project infrastructure and critical feedback. DB, SB; provided critical feedback to preprocessing and analysis. SB; study design and coordination. GFG and SB wrote the first draft of the article. All authors critically read and revised the article.

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#### Data and code availability

Further information and requests for resources (data and code) should be directed and will be fulfilled by the Lead Contact, Silvia Brem (sbrem@kjpd.uzh.ch). Some restrictions apply for data sharing for ethical reasons, because this would compromise participant confidentiality and privacy.

#### Declaration of Competing Interest

SW has received lecture honoraria from Opopharma in the last 3 years. Outside professional activities and interests of SB and SW are declared under the link of the University of Zurich: <https://www.uzh.ch/prof/apps/interessenbindungen/client/site/lang?lang=English>.

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#### 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.2021.100958>.

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