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**Developmental trajectory of neural
specialization for letter and number
visual processing**

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Developmental Science

Abstract

Adult neuroimaging studies have demonstrated dissociable neural activation patterns in the visual cortex in response to letters (Latin alphabet) and numbers (Arabic numerals), which suggest strong experiential influence of reading and mathematics on the human visual system. Here, developmental trajectories in the event-related potential (ERP) patterns evoked by visual processing of letters, numbers, and false fonts were examined in four different age groups (7-, 10-, 15-year-olds, and young adults). The 15-year-olds and adults showed greater neural sensitivity to letters over numbers in the left visual cortex and the reverse pattern in the right visual cortex, extending previous findings in adults to teenagers. In marked contrast, 7- and 10-year-olds did not show this dissociable neural pattern. Furthermore, the contrast of familiar stimuli (letters or numbers) versus unfamiliar ones (false fonts) showed stark ERP differences between the younger (7- and 10-year-olds) and the older (15-year-olds and adults) participants. These results suggest that both coarse (familiar versus unfamiliar) and fine (letters versus numbers) tuning for letters and numbers continue throughout childhood and early adolescence, demonstrating a profound impact of uniquely human cultural inventions on visual cognition and its development.

Keywords: Letter processing; number processing; event-related potential; high-level vision; development

Introduction

Literate adults possess dedicated regions in the visual cortex that are preferentially engaged in the visual perception of written characters such as letters and numerals (Cohen et al., 2000; McCandliss, Cohen, & Dehaene, 2003; Park, Chiang, Brannon, & Woldorff, 2014; Park, Park, & Polk, 2012; Roux, Lubrano, Lauwers-Cances, Giussani, & Démonet, 2008; Schlaggar & McCandliss, 2007; Shum et al., 2013). The fact that such cultural inventions elicit specific activation patterns in the visual cortex clearly demonstrates that visual experience alters the functional organization of the human brain (Dehaene et al., 2010; Park, Park, et al., 2012). Yet, little is known about the developmental time course of these experiential and cultural effects on functional neural organization.

In several recent functional magnetic resonance imaging (fMRI) and event-related potential (ERP) studies with adult participants (Park et al., 2014; Park, Hebrank, Polk, & Park, 2012), we demonstrated that visual processing of letters elicits greater neural responses compared to numbers in the left occipito-temporal region while visual processing of numbers elicits greater neural responses compared to letters in the right occipito-temporal region, thereby establishing a hemispheric double dissociation. Importantly, this dissociable pattern was observed in an experimental paradigm that minimized phonological and semantic processing and was observed early in the visual stream at the level of sensory-evoked visual N1 (or N1-latency) ERP component around 130–180 ms (Park et al., 2014), likely arising from lateral inferior occipital and/or ventral occipital temporal regions considering its latency and topographic distribution (Brem et al., 2009; Maurer, Brem, Bucher, & Brandeis, 2005; Rossion, Joyce, Cottrell, & Tarr, 2003; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999). Because letters and numbers are culturally determined, we proposed that, over the course of ontogenetic development, the early visual cortex in humans undergoes a major neural tuning for an effective processing of visual shapes of letters and numerals.

Here, we aimed to further investigate this hypothesis by mapping the developmental trajectory of the neural specialization for the visual processing of letters and numbers. On the one hand, most children in literate societies learn orthographic symbols and numerals in the preschool years (ages 3–5 y), and subsequently learn to read and write these symbols with proficiency in the first few years of elementary school. It is thus conceivable that the visual cortex becomes tuned to effectively distinguish these symbols in the early school years (ages 6–8 y). On the other hand, previous neuroimaging studies of reading have suggested that age-related changes in the neural responses to words compared to pseudowords and consonant strings continue into adolescence (Brem et al., 2006; Maurer et al., 2006; Maurer, Blau, Yoncheva, & McCandliss, 2010; Maurer et al.,

2005; Posner & McCandliss, 1992). Thus, it is also possible that effective neural tuning for visual processing of letters and numbers has a more protracted development.

To address this issue, we took a developmental cross-sectional approach and tested participants in four age ranges: 7, 10, and 15 year-olds, and young adults (college students). While a cross-sectional approach may be inadequate in capturing individual developmental trajectories, this approach is an important step in identifying the window of developmental change. Participants viewed strings of letters, numbers, and false fonts while we conducted high-temporal-resolution electroencephalogram (EEG) recordings of brain activity. We examined age differences in the neural dissociation between letter and number processing at the early visual processing level (as indexed by the amplitude of the N1-latency activity, a negative polarity ERP wave peaking around 160 ms after stimulus onset for these sorts of stimuli), which we reported previously to be the first—and the primary—latency point in adults that show a marked hemispheric dissociation between letter and number processing (Park et al., 2014). We further examined how the neural processing of unfamiliar visual stimuli differ from that of familiar stimuli by contrasting the ERP traces evoked by false fonts to the traces evoked by letters or numbers. In both contrasts (letters versus numbers and familiar versus unfamiliar stimuli), ERP patterns were similar in adults and adolescents but showed strikingly different patterns in 7- and 10-year-olds, suggesting a prolonged developmental trajectory for visual letter and number processing.

Materials and Methods

Participants

A total of 27 seven-year-olds, 30 ten-year-olds, and 30 fifteen-year-olds were recruited from the local community around Duke University, and 38 young adult participants (college students) were recruited from the Duke University psychology student subject pool. Data from one ten-year-old child was excluded, because he was unable follow instructions. Data from one college-student participant was excluded, because he fell asleep during the experiment (as monitored by a camera). See **Table 1** for the demographic information of the final sample. Note that 29 of the adults were tested with the same parameters as the 15-year-olds, while the remaining 8 adults were tested with the same parameters as the 7 and 10-year old participants (see *Stimuli and Task*).

Table 1. Demographic information, behavioral data, and selection of latency interval of interest (see *Electrodes of Interest and Statistical Analyses for the ERPs*).

Age Group	Number of subjects (females)	Age range (mean) in years	Expected school grade (in US)	Performance in the EEG task: Correct detection rate (mean \pm std)	Performance in the EEG task: Response time (mean \pm std)	N1-latency-adjusted interval: Right ROI	N1-latency-adjusted time interval: Left ROI
7-year-olds	27 (14)	6.5-7.5 (7.1)	2nd grade	78.6 \pm 12.7 %	835.2 \pm 124.0 ms	144-200 ms	120-232 ms
10-year-olds	29 (10)	9.5-10.5 (10.2)	5th grade	87.2 \pm 12.7 %	733.1 \pm 97.6 ms	139-192 ms	117-227 ms
15-year-olds	30 (16)	14.5-15.5 (14.9)	10th grade	96.2 \pm 3.4 %	535.7 \pm 51.1 ms	130-180 ms	110-213 ms
Adults	29 (15)	18.0-24.5 (19.3)	College	97.1 \pm 2.1 %	504.2 \pm 53.8 ms	133-184 ms	111-215 ms
Adults	8 (5)	19.5-26.5 (23.8)	College	91.4 \pm 10.4 %	617.8 \pm 119.2 ms	133-184 ms	111-215 ms

All participants were right-handed, had normal or corrected-to-normal vision, had no history of developmental disability, and were neurologically intact (screened by self or parental reports). All children and adolescent participants were also screened for native language to only include native English speakers; adult participants were not screened for this criterion. It should be noted that, in North Carolina where the study was conducted, children typically enter kindergarten at the age of five years, when formal education in literacy and numeracy begins. According to the NC standard curriculum, by the end of grade 1, children learn some basic competencies in reading and mathematics. For example, first graders master basic phonics and word-analysis skills in decoding words, learn to write opinion pieces and informative/explanatory texts, and understand place value, with ability to read and write numerals up to 120. Thus, all of our participants were expected to be able to recognize letters and numbers. Families of child and adolescent participants were compensated \$35-\$40 for their time and transportation; children (7- and 10-year-olds) were given a choice of a toy prize at the end of the study. The college-student participants were given departmental class credit for their participation in the study. All procedures were approved by the Duke University Institutional Review Board.

Stimuli and Task

Letters BCGKLSZ
 Numbers 1234567
 False Fonts J 4b-YC2Y

Figure 1. Stimuli set used in the study. Random combinations of letters, numbers, or false fonts were presented to participants. Participants passively viewed these stimuli, with the task to press a button in response to an occasional presentation of rightward or leftward arrows (or Pacman faces).

The stimuli were identical to the ones used in our previous study (Park et al., 2014). Four-character strings of consonant letters were created randomly from a set of capital letters “BCGKLSZ,” and four-character strings of numbers were created randomly from a set of Arabic numerals “1234567” (Figure 1). In addition, four-character strings of false fonts were created from a set of individual false-fonts that were generated by randomly rearranging features of letter and number stimuli (see Figure 1). The selection of letters, numbers, and false-fonts was chosen to roughly balance the physical properties between the stimulus categories in the number of straight or nearly straight lines, curved segments, enclosures, and joints. A monospace font face (Monaco) was used for all three conditions, and each character subtended approximately 0.57 x 1.17 degrees of visual angle.

Participants viewed character strings presented in random order in the center of the screen, occurring on top of a fixation dot that stayed continuously at the center of the screen. For 7- and 10-year-old children, the duration of the stimulus presentation was 500 ms with stimulus onset asynchronies (SOAs) varying randomly from 1,000 to 1,200 ms (uniform distribution). This stimulus duration was selected because children in a pilot experiment found the briefer 150 ms stimulus presentation frustrating, which discouraged them from continuing the experiment.

In order to ensure that children paid attention to the stimuli, a simple oddball detection task was imposed. Specifically, for 7- and 10-year-old participants, four simplified Pacman faces either pointing to the left or right occasionally appeared on the screen as one of the trials in the series of presented stimuli. When these Pacman faces appeared, participants were given a maximum of 3 seconds to discriminate whether the faces pointed left or right, using their respective left and right index fingers on a game controller. After a correct response, a smiley emoticon appeared briefly on the screen, paired with an auditory affirmative sound. After an incorrect response, a

frowning emoticon appeared briefly on the screen without any sound. This feedback was included to encourage young participants to maintain attention to the stimuli. Each child participant completed six blocks of trials, with each block consisting of 240 character strings (with the three stimulus categories in equal probability) and 16 oddball Pacman targets. Eight of the 38 adult participants were tested with task and stimulus presentation parameters identical to that used for 7 and 10 year-old participants.

The adolescent and adult participants underwent a very similar experimental procedure. All adolescents and 30 of the 38 adults were tested with 150 ms stimulus durations and with SOAs varying randomly from 600 to 800 ms, identical to the parameters used in Park, Chiang, Brannon, and Woldorff (2014). Participants were instructed to use their left and right index fingers on a game controller to detect the direction of arrowheads (i.e, left, <<<<, or right, >>>>) that occasionally appeared on the screen. The adult and adolescent participants were not given feedback about the accuracy of their response, keeping consistent with the paradigm in Park, Chiang, Brannon, and Woldorff (2014). Adult and adolescent participants completed a total of four blocks, each comprised of 360 strings and 24 oddball targets. All participants were given a set of practice trials at the beginning of the session to ensure they understood the oddball instructions. Each session took about 30 minutes of recording time.

Electrophysiological Recording

For all participants, the electroencephalogram (EEG) was continuously recorded using the ANT system (Advanced Neuro Technology, the Netherlands). A 32-channel customized, elastic electrode-cap was used for 7- and 10-year-olds, and a 64-channel customized, elastic electrode-cap was used for adults and adolescents. These custom caps (Duke32 and Duke64 Waveguard caps) have an extended coverage of the head from above the eyebrows to below the inion and have electrodes that are equally spaced across the cap (Woldorff et al., 2002). A more sparse montage of electrodes was used for younger participants given the challenge of child participant cooperation. Thus, whenever possible the ERP effects were examined and interpreted in the context of their entire topographic distributions in order to account for differences in the montage setup across age groups.

The electro-oculogram (EOG) was monitored with electrodes that were placed below the left eye and just lateral to the left and right canthi. The ground electrode was placed on the left collarbone. For 7- and 10-year-old participants, electrode impedances were maintained below 10k Ω for all channels. For adults and 15-year-old participants, electrode impedances were maintained below 10k Ω for EOG channels and below 5k Ω for all other channels. Due to the somewhat lesser patience in young participants for being capped, we allowed a slightly higher impedance threshold for the younger two groups as it enabled a significant reduction in capping time. According to a recent

study that systematically tested the effect of impedance on data quality (Kappenman & Luck, 2010), it is unlikely that these small differences in the impedance thresholds affect the quality of data in our study. Recordings were referenced online to the average of all channels and were digitized with a 512 Hz sampling rate per channel following an online anti-aliasing filter with a low-pass cutoff at 138 Hz (DC–138 Hz).

Electrodes of Interest

Given our central aim in investigating the age differences in the visual N1-latency component, which was previously established as being sensitive to letter versus number processing (see *Introduction*), analyses were done primarily at pre-selected occipital temporal electrodes of interest for this component. In the 64-channel recordings of adult and adolescent participants, two left (PO7i and PO9i) and two right (PO8i and PO10i) occipital temporal channels were selected based on our previous study (Park et al., 2014). These channels showed the largest ERP amplitude difference between the letter and number conditions around the N1 range in the previous study. Channels PO7i and PO8i are slightly inferior (about 0.14 radians) to PO7 and PO8 in the standard 10-20 system; channels PO9i and PO10i are also slightly inferior (about 0.11 radians) to PO9 and PO10 in the standard layout. These channels of interest are represented as white circles on the figures of the posterior perspective topographic maps shown in **Figures 2A-B**. The ERP traces from PO7i and PO9i were averaged together (denoted as PO7i/PO9i) to represent the ERPs over the left occipital region of interest (ROI), and the traces from PO8i and PO10i were likewise averaged together (denoted as PO8i/PO10i) to represent the ERPs over the right occipital ROI.

In 7- and 10-year-old participants where 32-channel caps were used, two channels closest to the combination of PO7i/PO9i and PO8i/PO10i were selected. In the left hemisphere, a channel slightly superior (about 0.19 radians) to PO7 in the standard layout was selected, henceforth referred to as PO7s, and a channel slightly medial to PO9 (about 0.14 radians) was selected, henceforth referred to as PO9m. In the right hemisphere, a channel slightly superior (about 0.19 radians) to PO8 was selected, henceforth referred to as PO8s, and a channel slightly medial to PO10 (about 0.14 radians) was selected, henceforth referred to as PO10m. PO7s/PO9m and PO8s/PO10m in the children's cap are represented as white circles on the figures of the posterior perspective topographic maps in **Figures 2C-E**.

Event-Related Potential Analysis

The continuous EEG data were first offline band-pass filtered from 0.01–100 Hz in asalab™ (www.ant-neuro.com). The rest of the event-related potential (ERP) analyses were conducted using the EEGLAB software package (Delorme & Makeig, 2004) and

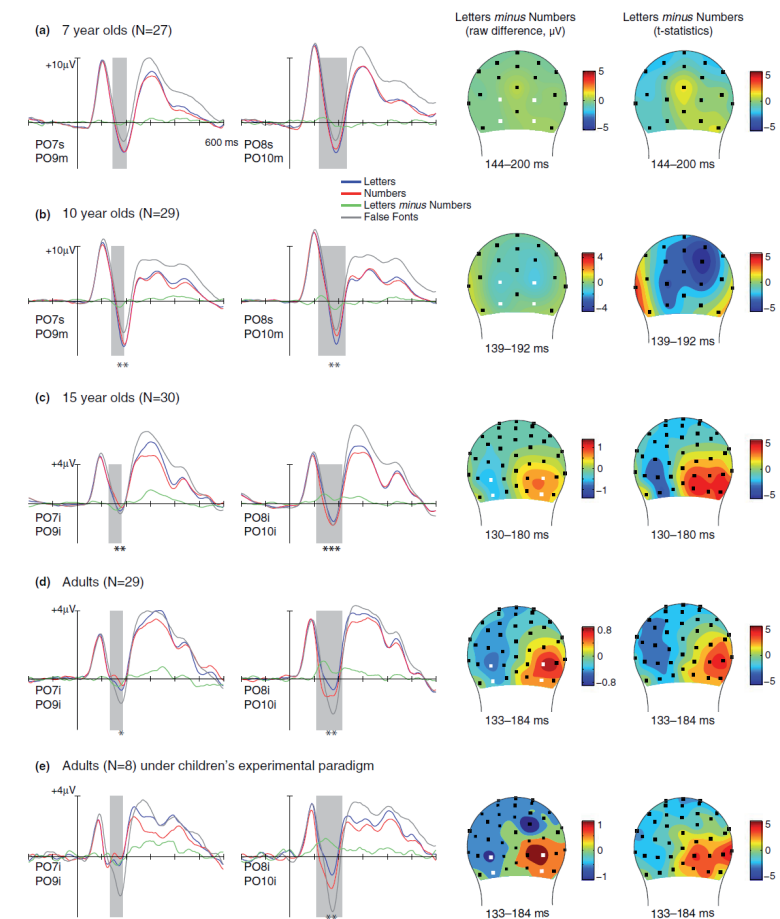


Figure 2. Grand-averaged ERP traces and posterior-perspective topographic maps (of both raw differential effects and t-statistics) representing the contrast of letters versus numbers in 7-year-olds (A), 10-year-olds (B), 15-year-olds (C), and adults (D). Data from an additional adult participants who underwent the exact same experimental paradigm as the 7- and 10-year-olds are presented in panel (E). Electrodes of interest for each age group are marked white in the posterior perspective topographic maps. For visualization of the corresponding differential ERPs across age groups, the ERP traces and raw-difference topomaps are scaled proportionately to the peak-to-peak distance from each age group's P1 to N1 components. Gray shaded areas indicate the pre-defined latency windows of interest in which the differential effects of letter versus number were tested; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The intervals of the topographic maps are derived from the overlapping time range that is covered by both the left and the right hemisphere channels' latencies of interest. Because the latency interval of interest in the left hemisphere was always within that observed in the right hemisphere, the topographic maps illustrate the mean ERP values of the entire latency interval in the left hemisphere channels but only the mean ERP values of part of the latency interval in the right hemisphere channels. Topographic distributions of other perspectives can be found in the Supporting Information.

the associated ERPLAB toolbox (Lopez-Calderon & Luck, 2014) in Matlab R2012a. As in our previous study (Park et al., 2014), the average of all channels was used as the reference (rather than, for example, the average of the mastoids) in order to provide more sensitivity for early visual components at ventrolateral posterior electrode. EEG epochs time-locked to the presentation of letter and number string stimuli were extracted from 200 ms before to 600 ms after the onset of the stimulus presentation, to which a pre-stimulus (-200 to 0 ms) baseline subtraction was applied. A step-like artifact rejection tool in EEGLAB was used to identify any trials in the data contaminated by eye movements or blinks (moving window width = 400 ms; moving window step = 20 ms; threshold = 45 μ V for adult and adolescent participants; threshold = 90 μ V for children participants). Epochs marked as artifacts were removed prior to averaging. The average artifact rejection rates were 20.2% for 7-year-olds, 13.9% for 10-year-olds, 13.7% for 15-year-olds, and 18.5% for adults. After time-locked averaging of the artifact-free epochs, the individual ERPs were low-pass filtered at 30 Hz, after which statistical analyses and grand averaging of the ERPs across subjects were performed.

Statistical Analyses for the ERPs

Latencies identified from our previous report (Park et al., 2014) were used to define the time window of interest in the present study. In that previous study, ERPs in adult participants (completely independent from the current sample) yielded a robust difference between letter- and number-evoked brainwaves in the left scalp ROI at 133–184 ms and in the right scalp ROI at 111–215 ms. From these results, we infer that the potential neural source(s) that are differentially activated by letters versus numbers can be captured in the brainwaves around these latency intervals. Thus, these same time windows were used in the present study for comparing the effects of stimulus type in adult participants. It seemed possible, or even likely, however, that these time windows would not be quite right for the waveforms in children and adolescent participants because age effects exist on ERP latencies (and amplitudes). Specifically, waveform peaks in these latencies ranges tend to occur later in younger participants, suggesting that the ERP component capturing a possible differential response for letters versus numbers would also be delayed in younger participants. Accordingly, we used the raw N1 latency difference across age groups as a proxy for the approximate amount of lag in the letter-versus-number differential effect in order to derive a best estimate of where the differential effect might occur in 7-, 10-, and 15-year-old participants. More specifically, in each age group, the latencies of the bilateral N1 peak were computed from the ERP collapsed across the letter and number conditions. For example, in 7 year olds, the N1 component peaked at 199 ms in the left ROI and at 191 ms in the right ROI, while in adult participants the peaks were 184 ms in the left and 178 ms in the

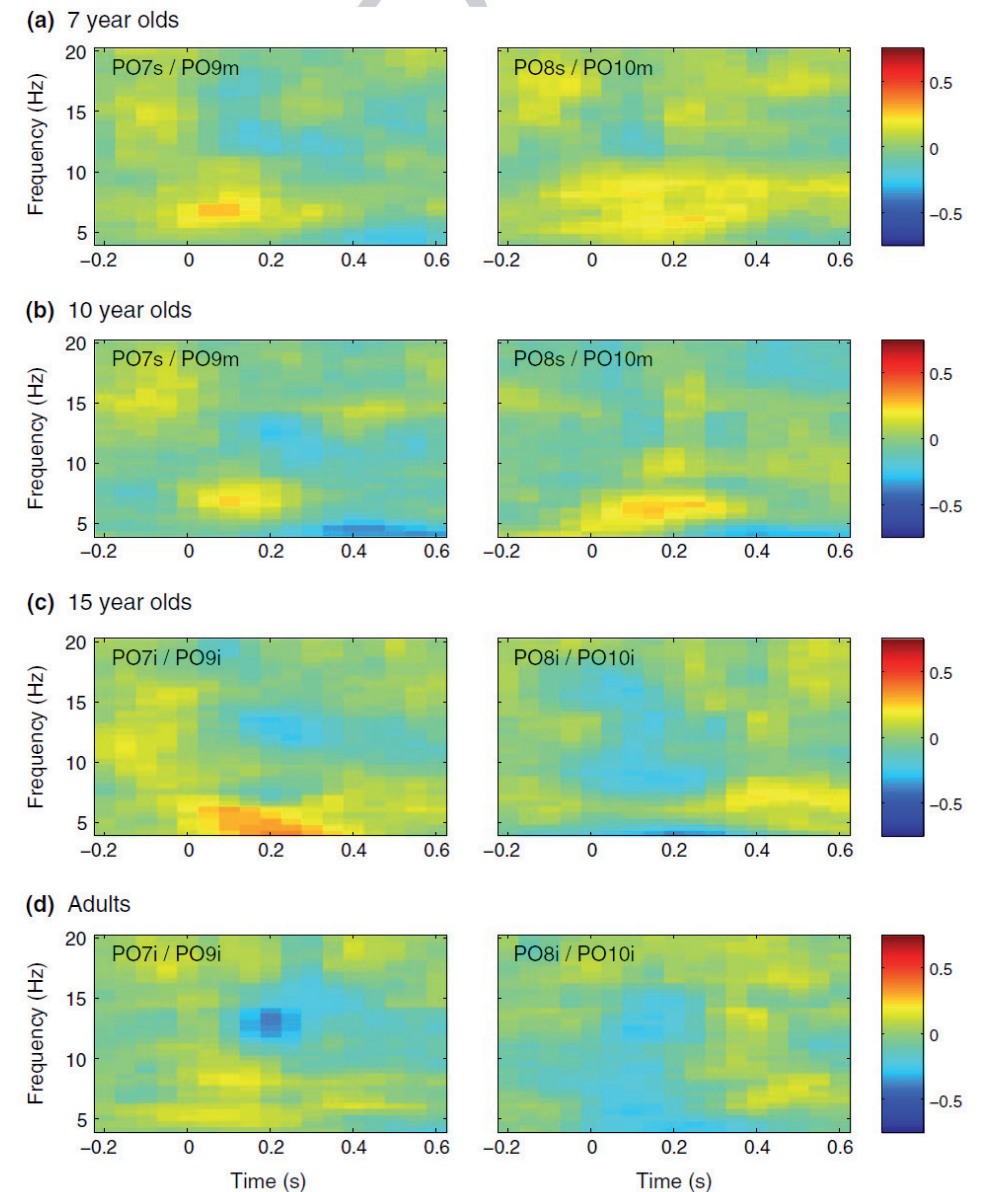


Figure 3. Spectral power of the brainwaves of the letter minus number contrast as a function of time and frequency in the electrodes of interest in 7-year-olds (A), 10-year-olds (B), 15-year-olds (C), and adults (D). Warm colors represents greater spectral power in the letter condition; cold colors represents the reverse. A cluster-based permutation testing was used to assess the statistical significance of the power spectra differences. Under the cluster alpha level of 0.05, no cluster was found to be significant in the entire time and frequency range of the spectral power.

right. (Note that the peak of the collapsed brainwave is different from the peak of the difference waves.) Then, the time windows used in adults were proportionately adjusted by multiplying the ratio between the N1 peak latencies of the target age group and the N1 peak latencies of the adult participants. For instance, in 7 year olds, the adjusted time window was calculated as the *adult time window* $[133\ 184] \times (199/184) = [144\ 200]$ in the left ROI and the *adult time window* $[111\ 215] \times (191/178) = [120\ 232]$ in the right ROI. The mean ERP amplitude within these N1-latency-adjusted time windows in each age group was used in the subsequent ERP analyses (see **Table 1**), and we refer to those effects as the “N1-latency amplitude” or the “amplitude of the N1-latency activity” in the remainder of this paper.

It should be noted that the peak ERP amplitudes vary by age. Therefore, for an accurate and fair visualization of differential ERPs across age groups (**Figures 2, 4, & 5**), the ERP traces and topomaps are scaled proportionately to the peak-to-peak distance (larger of the two ROIs) from each age group’s P1 to N1 components.

Time-frequency Analysis

In addition to the ERP extraction and analyses, frequency decomposition of the event-related oscillatory activity in the theta, alpha, and beta frequency bands was performed using a moving window discrete Fourier transform implemented by the FieldTrip software package (Oostenveld, Fries, Maris, & Schoffelen, 2010). Before the data were transformed to frequency power, a Hanning window was multiplied with the data segment of interest. The Hanning window had a width of four cycles in the theta range (4-7 Hz), five cycles in the alpha range (8-14 Hz), and seven cycles in the beta range (15-20 Hz). This resulted in a maximal temporal smearing of, for example at 10Hz, plus and minus 250 ms ($10\text{Hz} \times 2.5$ cycles on either side of the time point of interest). Frequency decomposition was performed separately on each channel of interest. Power (in μV^2) estimates of the different frequencies were extracted from 2 to 20Hz in steps of 0.5Hz and time points from -0.5 to 1.5 seconds in steps of 0.05 seconds.

Baseline correction of the power estimates was performed using a two-step method: first on the single trials by dividing the power estimate of each frequency for each time point by the mean of the power over all time-points for of that frequency (hence, resulting in the percentage activity relative to the whole trial). The resulting power was subsequently log transformed. ($\text{ERSP}_{\text{FullITB-dB}}$ as described by (Grandchamp & Delorme, 2011)). Finally, a pre-stimulus absolute baseline correction (-0.5 to -0.2) was performed on the grand-average ERSP. This method has been shown to be efficient in dealing with outliers and noise (Grandchamp & Delorme, 2011).

Statistical tests of frequency data were performed using a cluster-based permutation testing approach (Maris & Oostenveld, 2007). More specifically, t-tests were performed on

the power spectrum value for each frequency and time point of interest; if the resulting statistic exceeded a p-value of 0.05, then that time frequency point was included into a cluster that was formed by including significant adjacent points. Cluster statistics were obtained by summing all t-values within a cluster. Statistical significance of a cluster was obtained by comparing the cluster statistic to a permutation distribution (created by 1000 iterations by randomly switching the labels between conditions) at a cluster alpha level of 0.05.

Results

Performance on the oddball task was high for all age groups, indicating that participants were attentive during stimulus presentation (see **Table 1**). Between subjects one-way ANOVA revealed significant effects of group on these behavioral measures (Accuracy: $F(3,113) = 29.07$, $p < 0.001$; RT: $F(3,113) = 94.77$, $p < 0.001$).

Letters versus numbers

We first examined the differential ERP brainwaves between the letter and number conditions in the N1 time window. Note that the hypothetical neural processes differentiating the processing of letters, numbers, and similar orthography-like stimuli occurred in the N1-latency range (Park et al., 2014), which may be different from the raw N1 component itself (Luck, 2014). Thus, we use the term “amplitude of the N1-latency activity” to refer to these inferred neural processes in this paper. A repeated-measures ANOVA on the amplitude difference between letters and numbers was performed with hemisphere as within-subject and age group as between subject variables. This analysis revealed significant effects of age group ($F(3,111) = 4.408$, $p = 0.006$), hemisphere ($F(1,111) = 35.872$, $p < 0.001$), and a marginally significant interaction between age group and hemisphere ($F(3,111) = 2.551$, $p = 0.059$).

We then proceeded to test the N1-latency amplitude differences between letters and numbers in each age group. 7-year-old children revealed no differentiation in the N1-latency amplitude in the left or right ROIs for the letter and number strings (Left ROI: $t(26) = -0.517$, $p = 0.610$, Cohen’s d (standardized difference scores) = -0.099; Right ROI: $t(26) = 0.022$, $p = 0.983$, $d = 0.004$) (**Figure 2A**). In 10-year-old children, greater N1-latency amplitude for letters was observed both in the left ROI ($t(28) = -3.942$, $p = 0.000$, $d = -0.732$) and the right ROI ($t(28) = -1.881$, $p = 0.070$, $d = -0.349$) (**Figure 2B**), with no relative lateralization. In 15-year-olds, the left ROI elicited greater N1-latency amplitude for letters ($t(29) = -3.896$, $p = 0.001$, $d = -0.711$) and the right ROI elicited greater N1-latency amplitude for numbers ($t(29) = 4.568$, $p < 0.001$, $d = 0.834$). In young adults,

N1-latency amplitude was greater for letters in the left ROI ($t(28) = -2.438$, $p = 0.021$, $d = -0.453$) and was greater for numbers in the right ROI ($t(28) = 3.756$, $p = 0.001$, $d = 0.697$), consistent with our previous report (Park et al., 2014) (**Figure 2D**).

This pattern of results was robust to the selection of latency window intervals. In particular, one may wonder how having a rather longer latency-window interval in the right ROI may have influenced these results. We tested the same effects in the right ROI while using a shorter-duration analysis window (i.e., one comparable to that used for the left ROI). The results were qualitatively identical to the original results. There was little differential effect in 7-year-olds (interval of 149-202 ms; $t(26) = -0.219$, $p = 0.828$, $d = -0.042$); greater amplitude for letters in 10-year-olds (interval of 146-198 ms; $t(28) = -3.668$, $p = 0.001$, $d = -0.681$); greater amplitude for numbers in 15-year-olds (interval of 137-186 ms; $t(29) = 4.142$, $p = 0.000$, $d = 0.756$) and in young adults (interval of 138-188 ms; $t(28) = 3.530$, $p = 0.001$, $d = 0.655$). In addition, one may wonder if the null results in our 7-year-olds on the right ROI are due to the fact that the pre-defined latency window selection is largely misaligned with where the (letter vs. number) differential effect could be happening (170-300 ms in PO8s/PO10m in **Figure 2A**). However, adjusting our original latency interval to capture that potential differential effect still failed to demonstrate statistically significant differential effect between letters and numbers in the 7-year-olds' right ROI (interval of 170-282 ms; $t(26) = -1.707$, $p = 0.100$, $d = -0.328$). Differential effects between letters and numbers thus appear to be negligible in the 7-year-olds.

The topographic maps of the difference waves graphically display these differential effects across the age groups (**Figure 2**). Little to no difference was observed across the entire set of electrodes in 7-year-old children. In 10-year-old children, there was a greater effect of letters compared to numbers across many of the posterior channels, with little indication of relative lateralization. In contrast to these two patterns, marked and focally lateralized differentiation of the ERPs evoked by the two stimulus categories was observed in the bilateral occipital sites in 15-year-olds and young adults. Thus, examination of the entire scalp topography suggests that age-group differences in the N1-latency amplitudes in the two ROIs are not due to idiosyncratic selection of channels of interest or difference in the montage layout, nor the number of channels employed in the different age groups.

Given these marked age differences, it is important to consider whether the differences in stimulus presentation duration between the age groups (150 versus 500 ms) contributed to the results. To test this alternative hypothesis, we ran a small group of adult participants ($N=8$) on the exact same experimental paradigm that young children performed. **Figure 2E** illustrates the results from this small sample. As in the prior results (**Figure 2D**), there was a significant interaction of N1-latency amplitude

between condition and hemisphere ($t(7) = 4.346$, $p = 0.003$). In the left ROI, the N1-latency amplitude was non-significantly greater for letters ($t(7) = -1.857$, $p = 0.106$, $d = -0.657$), although with an effect size that was larger than the observed effect size in **Figure 2D**. In the right ROI, the N1-latency amplitude was significantly greater for numbers ($t(7) = 4.953$, $p = 0.002$, $d = 1.751$). These results indicate that the hemispheric dissociable pattern between letter and number perception is highly replicable and that the different patterns found in 7- and 10-year-olds (**Figures 2A-B**) versus adolescents and adults (**Figures 2C-D**) cannot be attributed to specific differences in the experimental paradigm.

Another potential alternative explanation arises from difference in behavioral performance in the oddball detection task. While oddball trials (Pacman/arrows) were excluded from the current analysis as the analysis only examined responses to the letters, numbers, and false fonts, it is conceivable that younger children paid less attention to the screen compared to older participants as indicated by somewhat lower oddball-detection accuracy. Negligible difference in the brainwaves across trial types in young participants could then result from a lack of attention to the stimuli. We tested this alternative hypothesis by constructing subsets of each age group to equate accuracy. Specifically, nine 7-year-olds with the highest accuracy were selected (greater than 66th percentile) which resulted in a mean (+- std) accuracy of 90.9% (+- 0.03). Ten 10-year-olds with intermediate accuracy were selected (greater than 33th percentile and smaller than 70th percentile) which resulted in a mean (+- std) accuracy of 90.9% (+- 0.03). Nine 15-year-olds with lowest accuracy were selected (smaller than 33th percentile) which resulted in a mean (+- std) accuracy of 93.1% (+- 0.05). With this modified analysis, accuracy did not significantly differ across the three subsets ($F(2,27) = 1.2$, $p = 0.318$). Note that young adult data were not included because selecting the subset with lowest accuracy still resulted in significantly greater accuracy than the other age group subsets. We then analyzed N1-latency amplitude difference between letters and numbers in each of these age group subsets, and the results were very similar to the original findings. Seven-year-olds showed no N1-latency amplitude difference between letters and numbers in the left ($t(8) = -1.042$, $p = 0.328$, $d = -0.347$) and right ($t(8) = 0.106$, $p = 0.918$, $d = 0.035$) ROI. Ten-year-olds also showed no significant difference between the two conditions in the left ($t(9) = -0.502$, $p = 0.628$, $d = -0.159$) and right ($t(9) = -1.344$, $p = 0.212$, $d = -0.425$). On the other hand, this sample of 15-year-olds still exhibited a greater N1-latency amplitude for letters in the left ROI ($t(8) = -3.129$, $p = 0.014$, $d = -1.043$) but for numbers in the right ROI ($t(8) = 2.650$, $p = 0.029$, $d = 0.883$). Thus, it is unlikely that differences in ERP patterns across the age groups are due to participants' behavioral performance in oddball detection.

The results described thus far suggest that ERP patterns that differentiate early

visual processing of letters and numbers in each hemisphere have not yet developed by 7 or even 10 years of age. We next explored whether there were other differences in the brain signal that were not phased-locked to the presentation of the stimuli and thus not well captured by ERP differences. To test this possibility, we performed a time-frequency analysis on the brainwave data focusing on the theta (4-7 Hz), alpha (8-14 Hz), and beta (15-20 Hz) frequency bands in the bilateral ROI sites. This analysis, however, yielded no statistically reliable differences between letters and numerals in either ROI in any of the age group (**Figure 3**). We did not find an observable effect in the frequency domain between letters and numbers, unlike in the case of the ERP results, which may be due to temporal and frequency smearing of the temporally concentrated ERP effects that gets diluted in the frequency space. Additionally, there was no observable difference in the alpha band, which is inversely associated with increased cortical engagement and attention (Jensen & Mazaheri, 2010; van den Berg et al., 2014; Worden et al., 2000a).

Letters and numbers versus false fonts

Our second analysis of interest was the contrast between familiar symbols versus unfamiliar symbols. To do so, we first conducted a three-way ANOVA with condition (letter, number, and false fonts), hemisphere (left ROI and right ROI), and age group (7-, 10-, 15-year-olds, and adults) on the N1-latency amplitudes. This analysis revealed significant effects of hemisphere ($F(1,111) = 11.026, p = 0.001$), hemisphere by group ($F(3,111) = 6.288, p = 0.001$), hemisphere by condition ($F(2,222) = 19.817, p < 0.001$), condition ($F(2,222) = 50.312, p < 0.001$), and condition by group ($F(6,222) = 27.570, p < 0.001$), but there was no significant effect of hemisphere by condition by group ($F(6,222) = 1.353, p = 0.235$). In a contrast analysis, we then assessed how the N1-latency amplitude for letters and numbers each differed from that for false fonts. The contrast of letters versus false fonts was significant ($F(1,111) = 85.215, p < 0.001$) as well as the interaction between this contrast and age group ($F(3,222) = 47.466, p < 0.001$). Likewise, the contrast of numbers versus false fonts was significant ($F(1,111) = 49.587, p < 0.001$) as well as the interaction between this contrast and age group ($F(3,222) = 24.772, p < 0.001$).

Observing the interaction between these contrasts and age group, we then examined N1-latency amplitude difference between letters/numbers and false fonts separately in each age group. In 7-year-olds, both letters ($F(1,26) = 99.767, p < 0.001$) and numbers ($F(1,26) = 61.746, p < 0.001$) showed greater N1-latency amplitude than false fonts. The same pattern was observed in 10-year-olds where both letters ($F(1,28) = 85.080, p < 0.001$) and numbers ($F(1,28) = 25.582, p < 0.001$) showed greater N1-latency amplitude than false fonts. In 15-year-olds, both letters ($F(1,29) = 0.228, p = 0.637$) and numbers ($F(1,29) = 0.715, p = 0.405$) did not differ from false fonts in their N1-latency

amplitudes, although there was a significant condition (numbers versus false fonts) by hemisphere interaction ($F(1,29) = 23.103, p < 0.001$). In young adults, false fonts elicited greater N1-latency amplitude than letters ($F(1,28) = 8.858, p = 0.006$) and numbers ($F(1,28) = 5.467, p = 0.027$), which was completely opposite to the pattern seen in the 7- and 10-year olds, and the interaction between condition (numbers versus false fonts) and hemisphere was significant ($F(1,28) = 5.360, p = 0.028$). Analysis from additional adult subjects who underwent the exact same paradigm as in younger children revealed a qualitatively identical pattern as the main group of adults, resulting in greater N1-latency amplitude for letters ($F(1,7) = 9.546, p = 0.018$) and numbers ($F(1,7) = 6.706, p = 0.036$) compared to false fonts, with a significant effect of condition (numbers versus false fonts) by hemisphere interaction ($F(1,7) = 14.533, p = 0.007$).

Examination of the differential brainwaves across the entire epoch revealed a better characterization of the developmental difference, as shown in **Figure 4**. In younger participants (7- and 10-year-olds), the differential brainwaves showed a slow, negative-going trend until around 300 ms from stimulus onset. In contrast, adolescent and adult participants' differential brainwaves showed a marked positive-going "flip" around the N1 time window for both the letters versus false fonts contrast and the numbers versus false fonts contrast. The topographic maps of the contrast waves give another perspective on these developmental changes (**Figure 4**), which showed slow negative-polarity waves in the bilateral ROIs in younger participants, while in adults there was a stark positive flip around 150–200 ms.

It might be worth considering whether slow negative-polarity waves at later latencies (see **Figure 4**), which was observed in all age groups, are related to the processing of an unexpected stimuli (as in P3, (Chapman & Bragdon, 1964; Sutton, Braren, Zubin, & John, 1965)) or to semantic processing (as in N400, (Kutas & Hillyard, 1980)). It should be noted that, although false fonts are novel to participants, the proportion of false font presentation was equal to that of letters and number, so they are not technically "unexpected" stimuli from any likelihood standpoint. Also, there was no linguistic context in the current study and that consonant strings and Arabic numerals should minimally evoke any semantics.

Finally, exploratory time-frequency analyses were run to examine the spectral power differences between the familiar (letters and numbers combined) and the unfamiliar (false fonts) visual symbols. As can be seen in **Figure 5**, theta and beta bands overall showed greater power for familiar stimuli in 7- and 10-year-olds. However, 15-year-olds and adults showed the opposite pattern with greater power for unfamiliar stimuli in the theta band with the peak centered around 200 ms. Given that visual evoked potentials around the N1 latency usually make a one-cycle sinusoidal wave in 200 ms

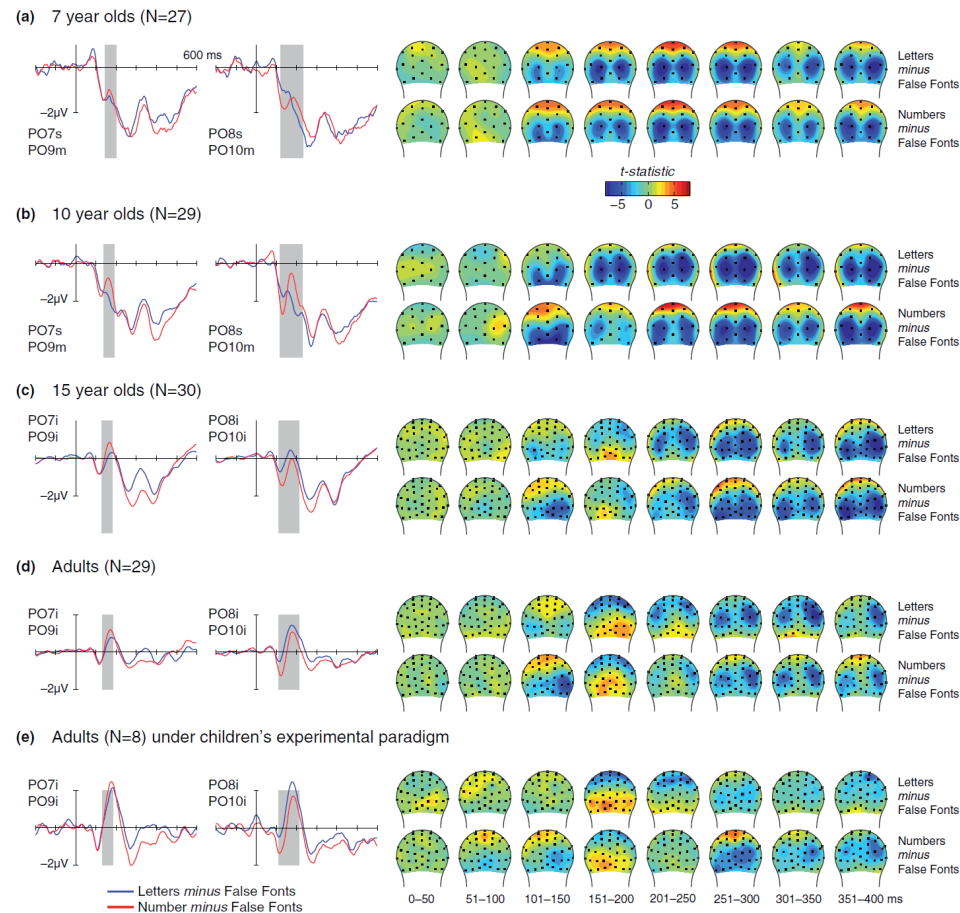


Figure 4. Grand-averaged ERP traces and posterior-perspective t-statistic topomaps representing the contrast of letters versus false fonts and numbers versus false fonts in 7-year-olds (A), 10-year-olds (B), 15-year-olds (C), adults (D), along with additional adult participants run in the identical paradigm as the two younger groups (E). Other conventions are identical to that in Figure 2. Topomaps of the raw difference values can be found in the Supporting Information.

(i.e., frequency of 5 Hz), some of these differences in theta (4-7Hz) spectral power may be explained by the presence of an N1-latency amplitude difference observed in the ERP analyses (Figure 4). An additional time-frequency analysis for which the evoked potential was removed from each epoch of the raw EEG data prior to the time frequency decomposition mainly confirms this conjecture (Figure 6). In addition, frequency spectra revealed more alpha (8-14 Hz) power for familiar versus unfamiliar stimuli following the theta or N1 modulation (from approximately 0.3 s to 0.7s), across all age groups.

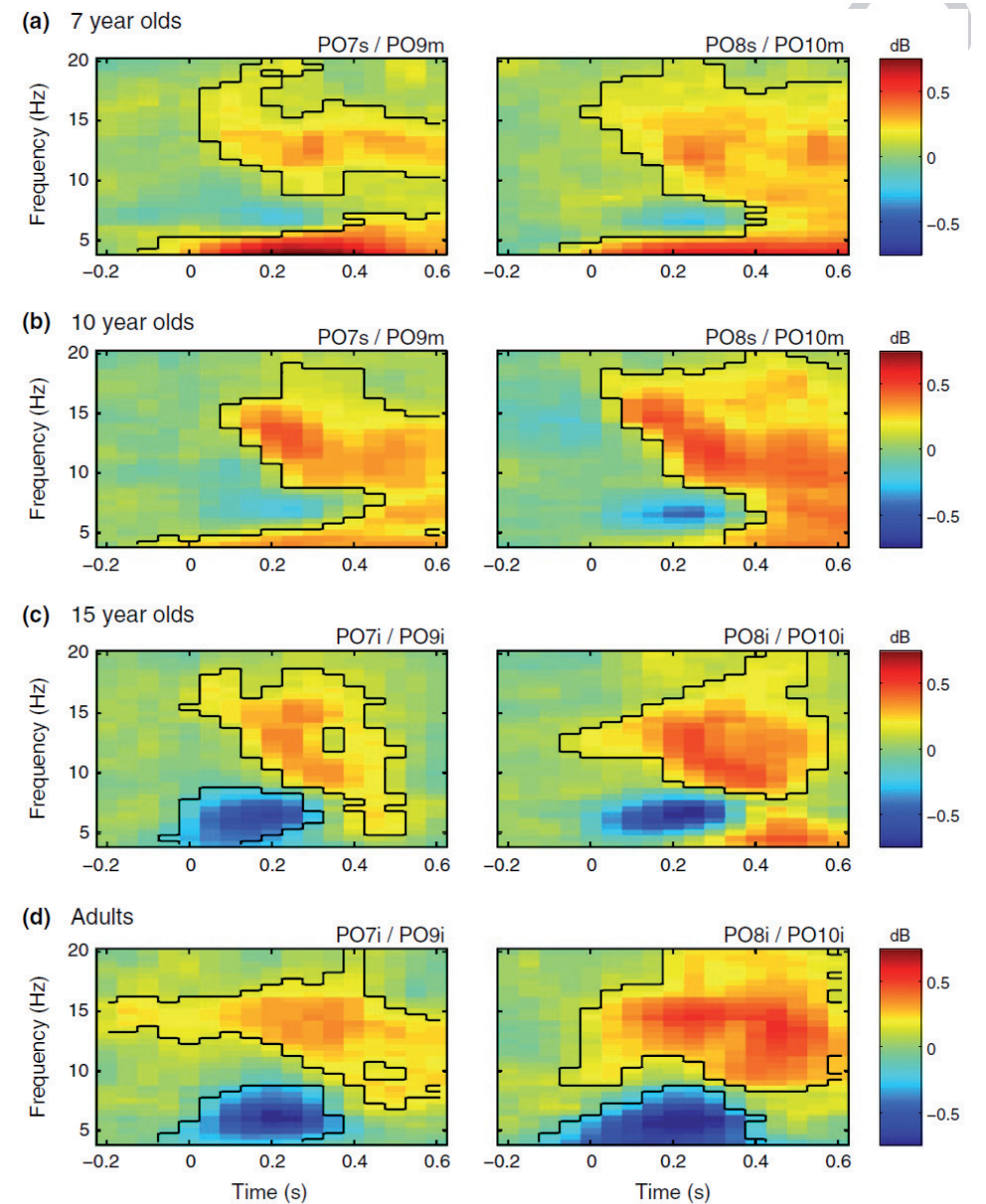


Figure 5. Spectral power of the brainwaves of the letter and number combined versus false fonts contrast as a function of time and frequency in the bilateral electrodes of interest in 7-year-olds (A), 10-year-olds (B), 15-year-olds (C), and adults (D). Time frequency points showing significant power spectra differences according to the cluster-based permutation testing method are outlined with black border. Fifteen-year-olds and adults showed an effect in the theta range where there was less theta power for familiar compared to unfamiliar stimuli.

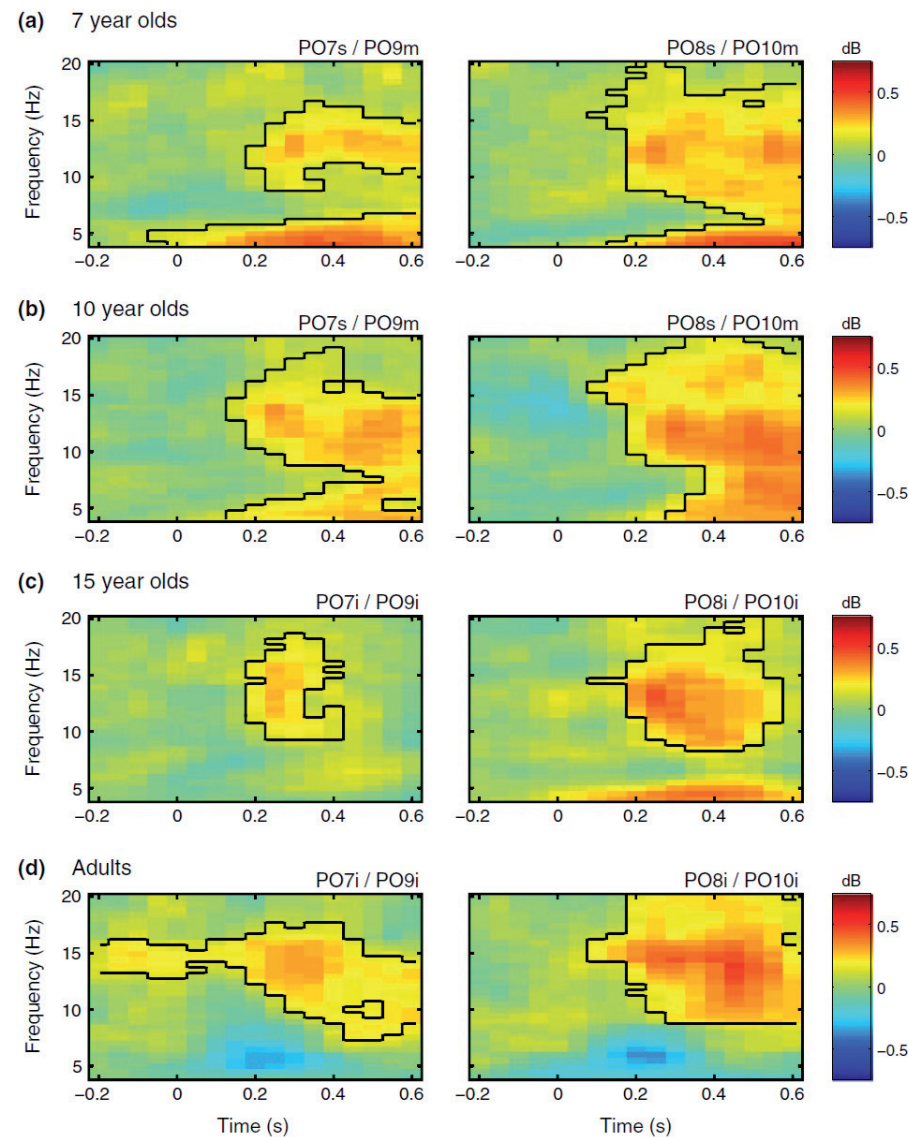


Figure 6. Time-frequency spectra contrast for letter and number combined versus false fonts with the contribution from the evoked potentials removed. The time-frequency spectra for each age group in which for every subject and every condition the average ERP was calculated and subtracted from the corresponding epochs prior to the time-frequency transformation of the EEG data. Time frequency points showing significant power spectra differences according to the cluster-based permutation testing method are outlined with black border. Most of the theta effect of letters and numbers combined compared to false fonts (cf. Figure 5) were removed after the evoked potential was subtracted from the EEG data prior to time-frequency transformation.

Discussion

Our study was designed to investigate the developmental emergence of the ERP dissociation that has been observed in adults between the visual processing of letters and numbers, as well as the dissociation between familiar (letters and numbers) and unfamiliar (false fonts) visual stimuli. We sought to identify the developmental time frame when the hemispheric double dissociation between letter and number processing emerges (Park et al., 2014).

In our youngest 7-year-old participants, the visual cortex showed negligible dissociation in either the N1-latency amplitude or in the power spectra between the letter and number conditions (Figure 2A). In contrast, the brainwaves evoked by letters or numbers in the 7-year-olds differentiated significantly from the brainwaves evoked by false fonts, both around the N1 latency and later (Figure 4A). These results indicate that by 7 years of age, the visual system is able to coarsely differentiate well-exposed familiar character symbols from unfamiliar ones starting at the earliest level of category-specific processing, but it is not yet tuned to make the finer distinction between letters and numbers. This is surprising given that 7-year-old children are expected to know how to read and write letters and numbers. Thus, these results suggest that the visual system requires much more extensive experience than just a few years of exposure and interaction with letters and numbers before it is able to show the rapid-differentiation processing pattern dissociating letters and numbers in adults (Maurer et al., 2005; Park et al., 2014; Park, Hebrank, et al., 2012).

A few previous studies have reported findings that are relevant to the current results in our youngest participants. In Maurer, Brem, Bucher, and Brandeis (2005), kindergarteners (approximately 6.5 year olds) were given a visual one-back task while they viewed words, pseudowords, symbols, and pictures (stimulus categories were presented in separate blocks). These children showed very little N1 differences between words, pseudowords, and symbol strings, although children with greater letter knowledge showed some sign of a right-lateralized N1 effect (greater N1 amplitude) for words compared to symbols (Maurer et al., 2005). Similarly, Posner and McCandliss, (1992) found that 10-year-olds, but not 4- and 7-year-olds, showed brainwaves that differentiated known words from unknown words and consonant strings at 200–300 ms.

A slightly different pattern was observed between word and symbol string processing in other studies. In one study (Brem et al., 2010), children prior to reading (mean age of 6.4 years) judged the presentation modality (visual/auditory) of words and arbitrary symbols, and these children showed greater N1 amplitude in response

to words compared to symbols, similar to what we report here¹. This study also found that this N1 amplitude difference increased after sessions of grapheme-to-phoneme correspondence training. In another study, children (mean age of 6.4 years) judged whether the presented word denoted an animal or judged whether the symbol string contained an asterisk (Bach, Richardson, Brandeis, Martin, & Brem, 2013), and they also showed greater N1 amplitude to words than to symbols bilaterally. Interestingly, this study found that greater N1 amplitude difference was associated with greater reading comprehension two years later. Yet another study in typically developing and dyslexic 8-year-olds showed that words elicit greater N1 amplitude than meaningless letter-like symbols do in a visual one-back task in both groups and that the difference in the N1 amplitude between words and symbols correlated with reading fluency in dyslexic but not in typically developing children (González et al., 2014).

The effects of these aforementioned studies differ to some extent (i.e., some studies reported greater N1 amplitude for words compared to arbitrary symbols and some did not), likely due to differences in subject population, experimental paradigm, and stimuli. Nevertheless, one may conclude from the collection of studies that N1 sensitivity to words compared to symbol strings, or coarse tuning to visual word forms, arise by around 6 or 7 years of age, and that this coarse tuning is predictive of reading ability.


Our current results advance the literature by examining the fine-tuning of the visual cortex to two equally prominent visual categories: letters and numbers. The fact that 7-year-olds' brainwaves at the N1-latency level do not dissociate letters and number is surprising, considering that these children (typically in 2nd grade elementary school in the U.S.) are clearly capable of behaviorally differentiating letters and numbers (see *Participants* under *Materials and Methods*). Perhaps even more surprising, the three additional years of exposure and experience with letters and numbers in the 10-year-olds are apparently still insufficient to mature the visual cortex to show the hemispheric double dissociation observed in adults. Instead of greater early sensory-processing sensitivity to letters in the left hemisphere and to numbers in the right as seen in adults (Park et al., 2014), 10-year-olds showed greater N1-latency negativity for letters compared to numbers in *both* the left and right posterior inferior channels (**Figure 2B**). By 15 years of age (**Figure 2C**), however, the ERP patterns were similar to that of adults, reflected by greater N1-latency negativity for letters in the left and for numbers in the right (**Figure 2D**). Overall, these data suggest that sensitivity at early processing levels to letters over numbers in the left occipital cortex emerges gradually from 7 years of age to adults. In

contrast, early neural sensitivity to numbers compared to letters in the right occipital cortex showed a more complicated developmental trajectory, wherein there was a reversal in the polarity of the number-versus-letter N1-latency at around age 10. One interpretation of the present results is that the tuning of the visual cortex for efficient processing of numerals is even more protracted than the tuning for efficient processing of letters. In a previous fMRI study (Park, Hebrank, et al., 2012), we found an overall right-lateralized neural sensitivity to Arabic numerals. Interestingly, the laterality of the activation pattern in the visual cortex for numbers was highly correlated across participants with the laterality of the activation pattern in the parietal cortex evoked by mathematical processing. Consequently, we had proposed that sensitivity to Arabic numerals in the visual cortex arises from the interactive top-down influence from the parietal cortex over development (Park, Hebrank, et al., 2012), just like the left-lateralized neural sensitivity to visual word forms is thought to arise from the interaction between the visual cortex and the left-lateralized language areas including the left perisylvian and inferior frontal areas (Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2008; Maurer & McCandliss, 2007). According to this line of reasoning, 10-year-olds may not have sufficient mathematical experience with Arabic numerals to drive neural tuning at the level of extrastriate cortex that can drive rapid neural differentiation of such stimuli. Neural sensitivity to numbers at early processing levels may emerge only after much more extensive education in mathematics between ages of 10 and 15. Given that our stimuli consisted of four-digit numbers (and four-letter strings), it is possible that children's conceptual understanding of multi-digit numerals might contribute to this developmental pattern. Previous studies have shown that 9-year-olds' estimation of numbers in a 0-10,000 number line is relatively immature, and it is not until children become 12 years old when they show an accurate, linear representation of four digit numbers (Booth & Siegler, 2006; Thompson & Opfer, 2010). Thus, the 10-year-olds in our study, compared to the 15-year olds, may not have had the cognitive capacity to automatically process four digit numerals. On the other hand, such an account would be difficult to explain the reversal in the polarity of the differential N1 at age 10. This interpretation of protracted development is consistent with recent findings in reading development, such as letter-speech sound integration (Froyen, Bonte, van Atteveldt, & Blomert, 2009; Žarić et al., 2014) and sensorimotor representations of word categories (Dekker, Mareschal, Johnson, & Sereno, 2014).

One limitation of the present study is that we did not collect detailed demographic data nor did we assess academic competence. In the future, it would be valuable to test how children's academic achievement and experience can inform us about the developmental differences in the cortical sensitivity to fine-tuning of letters and number.

The observed ERP dissociation between familiar (letters and numbers) and unfamiliar (false fonts) visual stimuli demonstrates a second interesting qualitative developmental

¹ In that study (Brem et al., 2010), however, two different participant groups who received different cognitive training orders showed different ERP patterns even prior to any training: One group showed a greater N1 amplitude for words compared to symbols in the left occipital site, while the other group showed a greater N1 amplitude for words compared to symbols in the right occipital site.



change between ages 10 and 15. The ERPs of our younger participants (7- and 10-year-olds) showed a marked difference in the brainwaves evoked by familiar versus unfamiliar stimuli starting as early as 100 ms, with the familiar stimuli showing consistent enhanced ERP negativity across much of the epoch (**Figure 4A & 4B**). This pattern likely reflects a coarse neural tuning to familiar written characters (in terms of orthography and possibly phonology) from completely novel stimuli. This pattern, however, changes dramatically in 15-year-olds and adults. The contrast waves of familiar minus unfamiliar stimuli show a prominent positive deflection around 150-200 ms, which is also evident in the topographic maps (**Figure 4C & 4D**). Such an age-group difference was still observed from additional adult participants who underwent the identical experimental paradigm as the young children (**Figure 4E**) and was still observed when subsets of participants were analyzed to equate the accuracy in the oddball detection task (see **Results**). Note that this developmental change between 10 and 15 years of age seems gradual and quantitative, unlike the contrast of letters and numbers in which 7-, 10-, and 15-year-olds all show qualitatively different ERP patterns (**Figure 2**).

Greater N1-latency amplitude for false fonts replicates our previous report in adults (Park et al., 2014), an effect we had interpreted as reflecting greater need for neural resources to automatically engage in parsing unfamiliar stimuli (also see Appelbaum, Liotti, Perez, Fox, & Woldorff, 2009). According to this interpretation, the visual cortex in our younger participants (7- and 10-year-olds) does not automatically engage at early processing levels to extract and parse visual features. These relatively early latency enhancements were followed by lower alpha power for all age groups for unfamiliar stimuli. Alpha power has been inversely associated with increased cortical engagement and attention (Jensen & Mazaheri, 2010; van den Berg et al., 2014; Worden et al., 2000a), suggesting that unfamiliar stimuli recruited more cognitive engagement at a later processing stage, perhaps to try to make sense of those unfamiliar stimuli. Strikingly, there was lower alpha power for unfamiliar stimuli across all age groups, suggesting that even though younger participants process familiar and unfamiliar stimuli similarly at an early processing level, they do recruit more cognitive resources later for processing unfamiliar stimuli. If this explanation is true, then understanding the mechanism that allows young brains to bypass an automatic engagement of unknown visual features will be an important avenue for future research, particularly because such print sensitivity may be related to reading abilities in children (e.g., (Bach et al., 2013; Brem et al., 2010; González et al., 2014)).

In summary, the results indicate that there is a prolonged developmental trajectory in the maturation of the visual system for processing letters and numbers. These data provide an important step to understanding the role of experience with reading and mathematics in shaping the human visual cortex and its functional processing.