

Early dissociation of numbers and letters in the human brain

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Abstract

Numbers and letters are culturally created symbols which are learned through repeated training. This experience leads to a functional specialization of the perceptual system of our brain. Recent evidence suggests a neural dissociation between these two symbols. While previous literature has shown that letters elicit a left lateralized neural response, new studies suggest that numbers elicit preferentially a bilateral or right lateralized response. However, the time course of the neural patterns that characterize this dissociation is still underspecified. In the present study, we investigated with magnetoencephalography (MEG) the spatio-temporal dynamics of the neural response generated by numbers, letters and perceptually matched false fonts presented visually. Twenty-five healthy adults were recorded while participants performed a dot detection task. By including two experiments, we were able to study the effects of single characters as well as those of strings of characters. The signal analysis was focused on the event related fields (ERF) of the MEG signal in the sensors and in the source space. The main results of our study showed an early (<200 ms) preferential dissociation between single numbers and single letters on occipito-temporal sensors. When comparing strings of numbers and pseudowords, they differed also over prefrontal regions of the brain. These data offer a new example of acquired category-specific responses in the human brain.

Introduction

Numbers and letters are culturally created symbols that become meaningful only after extensive training -- they have no significance to infants or illiterate adults (Dehaene & Cohen, 2007; Hamilton et al., 2006). The ability to recognize these constructs involves a functional preference of cognitive and perceptual systems and thus, offers a new example of acquired category-specific responses in the human brain.

Neural categorization of visual stimuli elicits a cascade of processes along the first hundreds of milliseconds after the presentation of the stimuli (Rossion et al., 2003; Tanaka et al., 1999). In the context of word forms, sublexical processing and orthographic-to-phonological conversion occur in early latencies after the stimulus onset (between 100-200 ms and 200–300 ms, respectively), whereas lexical access and semantic retrieval occur in later time-windows (between 300–400 ms and after 400 ms respectively) (Grainger and Holcomb 2009; Bann & Herdman, 2016; Hauk et al., 2008). Specifically, visual encoding of letter/word forms occurs early around 130 ms from stimulus onset preferentially in the left ventral visual stream (McCandliss et al., 2003; Appelbaum, Liotti, Perez, Fox, & Woldorff, 2009; Schendan, Ganis, & Kutas, 1998). Differential anatomical and temporal patterns have been observed between single and strings of letters in later latencies (James et al., 2005; Park et al., 2012). However, further evidence at better temporal and anatomical resolution, and full-coverage methods would be valuable.

Recent evidence shows that the number-related pattern of neural activity dissociates from that of letters early during the first encoding levels in occipito-temporal regions of the brain (Park et al., 2014; Abboud et al., 2015; for a review see Hannagan et al. 2015). However, there is a lack of consistency regarding the hemispheric preference for such a dissociation. On the one side, opposite hemispheric recruitment of neurons has been evidenced for these two categories (Park et al., 2012). In an EEG study, Park et al., (2014) showed that while single numbers elicited increased EEG evoked responses compared to single letters on right hemispheric electrodes, the last evoked a similar pattern on left hemispheric electrodes. Both dissociations occurred in the time range of the N1 (between 140-170 ms). By examining also the neural response to strings of characters, the authors showed that strings of letters elicited a left lateralized response around 250 ms (in the range of the P2) when comparing with strings of numbers. Similar hemispheric lateralized

1 patterns for number and letter processing were observed in a source reconstruction in a
2 magnetoencephalography (MEG) study performed by Carreiras et al., (2015). On the
3 other hand, recent data shows that, instead of the unique right hemispheric specialization,
4 numerals recruit populations of neurons in both hemispheres, bilaterally. In an fMRI
5 study, Grotheer et al., (2016) observed a bilateral preferential response for numbers at the
6 inferior temporal gyrus (ITG) when comparing with letters, false numbers or everyday
7 objects. Similarly, Shum et al. (2013) observed with iEEG (intracranial
8 electroencephalography) a region in the right that responded preferentially to numbers.
9 Even though the coverage of the electrodes included mainly the right hemisphere, they
10 found similar results in the left hemisphere as well.
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19 Scientific work focused on the neural fingerprints of number processing has
20 received less attention. Arabic digits have typically been used as control stimuli when
21 studying letter- and word-specific neural activity. Also, to date, the handful of informative
22 literature has included fMRI, EEG focusing on a limited number of electrodes, MEG
23 restricting the analysis to regions of interest at the source space, and iEEG covering areas
24 of the right hemisphere mainly. However, as far as we know, none of these studies have
25 investigated the temporal dynamics and anatomical preferences of single and strings of
26 numbers with a non-invasive technique which includes a high temporal and spatial
27 resolution with MEG (by covering the whole head with 306 sensors), and including
28 sensor and source localization procedures and individual MRIs. Such an approach is
29 important since the encoding and dissociation of visually presented stimuli potentially
30 occurs on a millisecond scale and involves a variety of regions of the brain.
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42 The purpose of the present study was to investigate the temporal dynamics and the
43 anatomical localization of the dissociation of the neural evoked response to visually
44 presented numbers, letters and false-fonts. To do so, we studied (in two experiments) the
45 MEG signal in response to single numbers, letters and false fonts (Experiment 1), and
46 strings of numbers, pseudowords and strings of false fonts (Experiment 2) in young adults
47 during a dot-detection attention task. The task required participants to respond whenever
48 a dot was presented (catch trials) among the stimuli. This low-level task was selected
49 because it does not require explicit semantic or phonological processing but nevertheless
50 ensures attention during the task. This way, participants can apply the same processing
51 strategy for both numbers and letters, thus allowing direct comparison of these two
52 conditions. This task has been used previously (Dehaene in Science 2010; Carreiras et al., 2015)
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so that it captures better the natural processing of the stimuli without requiring explicit additional processes such as lexical decision or semantic categorization.

In our analysis, first, we studied the stimulus evoked MEG signal in the sensor space. This analysis allowed us to estimate the time-window(s) where dissociations between the stimuli occur. Based on the previous evidence reported above and the data reported here, we suggest that numbers and letters can dissociate at early latencies during the first time-windows of the visual encoding (<200 ms after stimulus onset). We also show that single items and strings of stimuli can elicit differential neural patterns around 250-300 ms (Dehaene, 1995; Park et al., 2014). Second, we computed the source localization of these evoked responses and focused the analysis on the time-windows which were the most prominent in sensor space. This analysis allows us to estimate the source locations where the dissociation of numbers occurs.

MATERIALS AND METHODS

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Participants. 28 young adults were recruited for the present study (Park et al., 2014; Carreiras et al., 2015). From this initial sample, 3 participants were excluded due to a technical difficulty during acquisition. The final sample included a total of 25 participants (24+/-3 years of age). All of them reported to be native speakers of Spanish, right handed and free of neurological disease (criteria for participation established prior to data analysis). All participants gave their written informed consent in accordance with guidelines approved by the Research Committees of Basque Center on Cognition, Brain and Language. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

Experimental design

Two experiments were administered in this study using Psychtoolbox. Both experiments included a visual detection tasks (Figure 1) and differed between them only in the stimuli.

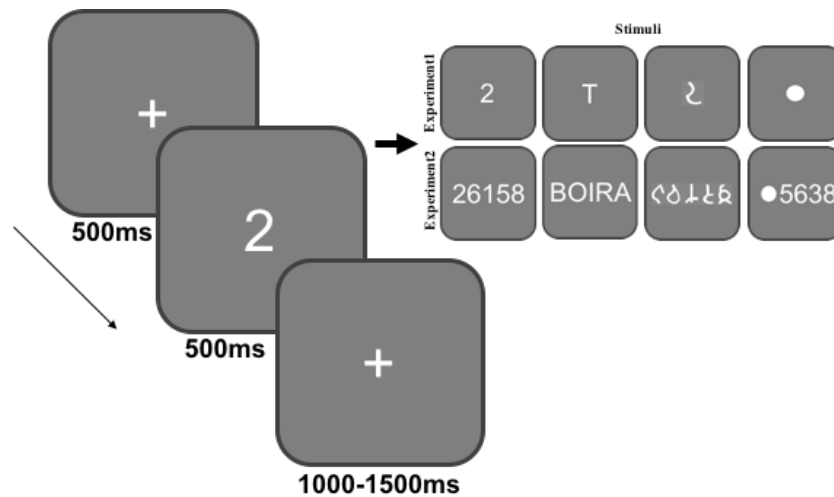


Figure 1. Visual detection task (left panel). Participants were instructed to attend to the stimuli and make a button press whenever a dot was presented. (b) Stimuli used in Experiment 1 (single numbers, single letters, single false-fonts and dot-detection) and in Experiment 2 (strings of numbers, pseudowords, strings of false-fonts and dot-detection).

Experiment 1. Participants were presented with three types of single stimuli (numbers, letters and false fonts). The numbers included digits from 1 to 9, and the letters were A, C, D, F, L, P, S, U and V. Following the procedure by Shum et al., (2013), the false fonts were created from rearranged numeral and letter stimuli, with the number of pixels, angles, and curves kept as similar as possible while ensuring that the stimulus remained unrecognizable.

Experiment 2. The second experiment mimics the first with the difference that it included strings of stimuli (strings of numbers, pseudowords and strings of false fonts) instead of single-character stimuli. Each string included 5-6 letters, numbers, or false fonts. The strings of numbers consisted of combinations of digits between 1-9. Phonotactically legal pseudowords were used instead of consonant strings since the first could be clustered in a unified readable item, similar to what happens with number strings. The pseudowords were the following: ASIMA, BOIRA, DOBECA, DOCHAS, EGALO, MODRO, PLETAR, TEPOR, TOLAS.

For both experiments, the stimuli were presented in the center of the screen in a white font (Arial capital letters, covering not more than 1° of visual angle on the screen positioned ~ 1 meter far from the participant) on a grey background. Each stimulus was repeated 22 times resulting in a total of 198 stimuli per condition.

1 The trial started with a 500 ms baseline followed by the presentation of the stimuli for
2 500 ms. After the stimulus offset, an intertrial interval varied between 1000-1500 ms and
3 participants were invited to blink during this period. Participants were instructed to attend
4 to the stimuli and report with a button press whenever a dot (catch trial) was presented.
5 The catch trials were included in both experiments in order to ensure attention during the
6 tasks. For Experiment 1, catch trials consisted of a sole dot, whereas for Experiment 2
7 the catch trials consisted of a string of numbers/letters/false fonts (depending on
8 condition) and a dot (see Figure 1). During the entire experiment, participants were
9 instructed to make a button press whenever a dot was present as a stimulus. This allowed
10 us to ensure that participants were attending to the stimuli. The catch trials involved 10%
11 of the total trials and were not included for the MEG signal analysis. Participants with
12 accuracy lower than 80% in the catch trials would be excluded from the analysis.
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23 The stimuli within each experiment were presented in random order. Participants were
24 instructed to fixate on the center of the screen (fixation cross or stimulus) during the entire
25 task.
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29 **Data acquisition**

30 MEG data was continuously recorded (1000 Hz sample rate, 0.01–330 Hz online filter)
31 during the performance of the attentional task using a 306-channel (102 magnetometers
32 and 204 planar gradiometers) system (Elekta©, VectorView) placed in a magnetically
33 shielded room (Vacuumschmelze GmbH, Hanau, Germany) at the Basque Center on
34 Cognition, Brain and Language (Donostia-San Sebastián, Spain).
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42 Individual head shapes were obtained by using a three-dimensional Fastrak digitizer
43 (Polhemus). In addition, four head position indication (HPI) coils were placed in each
44 subjects' head: two in the mastoids and two on the forehead. The HPI coils provided
45 continuous head position estimation during the recording.
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50 For source reconstruction, a high-resolution 3D structural MR image (T1-weighted
51 MPRAGE sequence) was acquired with a 3T Trio MRI scanner (Siemens, Munich,
52 Germany) to the individual participants. Due to technical reasons, we obtained MRI scans
53 of 20 participants. For the remaining 5 participants, we used the MNI template MRI
54 provided by Fieldtrip (see reference below).
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Data analysis

Both experiments were analyzed similarly. Maxfilter software (version 2.2., Elekta Neuromag) was used offline to reduce external noise and compensate for head movements (temporal extension of the signal space separation method; Taulu and Kajola, 2005; Taulu and Simola, 2006).

The data analysis of the MEG signal was performed using the Fieldtrip Matlab toolbox for EEG/MEG analysis (Oostenveld et al., 2011; <http://www.ru.nl/neuroimaging/fieldtrip>). The analysis was conducted on the gradiometers. Only epochs free of button responses were included in the analysis. Automatic artifact rejection was applied to remove trials containing SQUID jumps and muscle activity. Independent component analysis (ICA) was used to visually detect and discard eye blinks and electrocardiogram activity from the MEG signal (“runica” algorithm implemented in FieldTrip/EEGLAB). The ICA procedure applies a linear decomposition to the data after which the data is represented as components. First, these components are visually inspected in a trial-by-trial basis and then, the trials affected by the artifacts are identified and rejected from the data. This procedure excludes the bad components and projects back the signal free of artifacts. The data was band-pass filtered between 1 and 35 Hz, demeaned, detrended and segmented between 300 ms before and 500 ms after the stimulus onset (resulting in epochs of 800 ms).

Sensor level analysis. The artifact-free signal was baseline corrected (with a 200 ms time-window prior to stimulus onset) and averaged across trials resulting in an event related (ERF) for each sensor, condition and participant.

Statistical analysis. Paired-sample t-tests (two-tailed) were used to test the null hypothesis of no difference between the different conditions (numbers vs. letters, numbers vs. false fonts and letters vs. false fonts) in time and sensor locations. In order to control for the family-wise error rate in the context of multiple comparisons over time points and sensors, a cluster-based nonparametric permutation statistic was performed (Maris & Oostenveld, 2007). Accordingly, clusters of channels and time samples with significant differences ($p < 0.025$) were created by temporal and spatial adjacency. A set of 1000 permutations was created by randomly assigning condition labels and then t values were computed for each permutation. A cluster was considered to have a statistically significant effect if the sum of t-values in the original dataset was greater than

1 the 95th percentile ($p < 0.05$) of the distribution of the corresponding values in the
2 randomized data. This analysis allowed us to establish the time-window(s) of interest for
3 a following post-hoc two-tail paired-sample t-test. The resulting significant time-
4 window(s) were selected for the analysis at the source space.
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8 We would like to note that although our findings are based on relatively common analysis
9 procedures, recent papers have suggested that the standard statistical practice cannot grant
10 conclusions about the experimental question under debate (Button et al. 2013; Gelman &
11 Carlin, 2014; Greenland et al. 2016; Wasserstein & Lazar, 2016; Benjamin et al. 2018;
12 Lakens et al. 2018; Sassenhagen & Draschkow, 2019). The present results should be taken
13 heuristically and the results of our exploratory analyses might be useful for planning
14 future pre-registered studies of the same phenomena. Interested readers are encouraged
15 to examine the data provided with this manuscript.
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23 **Source level analysis.** Source reconstruction analysis was performed in order to localize
24 the source of origin of the effects observed at the sensor level. For that aim, first a single-
25 shell head model was constructed from the anatomical MRI. A template grid with 3 mm^3
26 spacing was constructed using a MNI template brain. Then, single subject grids were
27 produced by warping the individual anatomical scans to this template and applying the
28 inverse warp to the template grid. This produced source- level data aligned across subjects
29 in MNI space.
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37 Source reconstruction of the MEG signal was performed with Linearly Constrained
38 Minimum Variance Beamformer (Zhang and Liu, 2015) following a common filter
39 approach. The spatial filter's coefficients were obtained from the average covariance
40 matrix from trials belonging to the three conditions. The resulting spatial filter
41 coefficients were then applied to each condition separately. This procedure results in a
42 power estimate per source location, time, condition and participant.
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49 **Statistical analysis.** The statistical analysis at the source space was focused on the time-
50 windows and contrasts showing the significant effects at the sensor level. To quantify the
51 differences in power between these significant contrasts, paired-sample t-tests (one-
52 tailed) were used ($p < 0.05$). A cluster-based permutation approach was used in order to
53 control for multiple comparisons over grid points (as explained above). The same caution
54 about the statistical results applies for the source analysis as above.
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1 **Effect size.** Effect size (Cohen's d) was computed to test the magnitude of the effects
2 between the conditions in the sensors and in the source space with the following formula:
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$$4 \quad d = (\mu_2 - \mu_1) / \sigma$$

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7 where μ_2 and μ_1 are the condition means and σ is the pooled standard deviation of the 2
8 conditions. The pooled standard deviation was calculated as follows:
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$$10 \quad \sigma = \sqrt{(sd1^2 + sd2^2)/2}$$

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13 where $sd1$ and $sd2$ are the standard deviations of the means of each condition.
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19 In order to offer a complete view of the data, we also depict the means (M),
20 standard deviations (SD), effect sizes and correlation values of the three conditions
21 (numbers, letters, false-fonts), that result in the significant topographies (sensors) and
22 latencies (time-windows) after contrasting the conditions statistically. For example, the
23 data “comparison 1: numbers [M=.13⁻¹¹; SD=.75⁻¹²] versus letters [M=.09⁻¹¹; SD=.69⁻¹²],
24 time-window: 124-208 ms, effect size: -.54, $r=.91$ ”, is calculated by taking the raw-
25 processed data (the data before calculating the statistics) and selecting the specific sensors
26 and time-windows which resulted statistically significant when applying the statistical
27 procedure. This procedure offers an overview of the raw-processed data just at the
28 significant sensors and time-windows.
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39 **Results**

40 **Behavior**

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44 *Experiment 1.* Participants on average responded to the catch trials with a 94±10 percent
45 accuracy and with a 495±125 ms delay (M±SD).
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49 *Experiment 2.* Participants on average responded to the catch trials with a 97±3 percent
50 accuracy and responded with a 489±144 ms delay (M±SD).
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Magnetoencephalography

Experiment 1. Sensor space

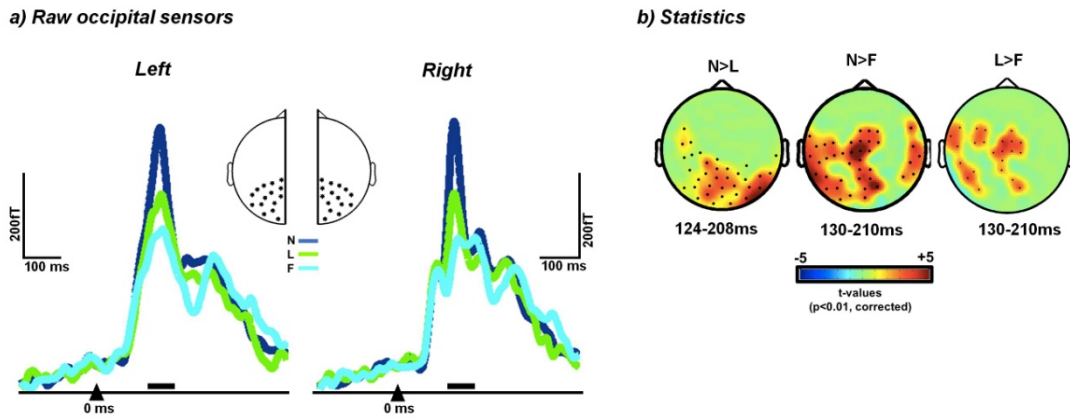


Figure 2. Experiment 1 sensors. a) **Raw occipital sensors.** Raw event related fields (ERF) averaged over the occipital sensors (left and right separately) for visualization purposes (dark blue: single numbers; green: single letters; light blue: single false fonts). The black triangle indicates the stimulus onset (0 ms). The black rectangle indicates the timing of the three significant time windows (124-208 ms, 130-210 ms and 130-210 ms) resulting from the t statistics between the conditions ($p < 0.01$, corrected). b) **Statistics.** Topographies of the distribution of the significant **t-statistics** at the sensor level (N>L: single numbers greater than single letters; N>F: single numbers greater than single false fonts; L>F: single letters greater than single false fonts). Dark dots display the significant sensors resulting from the paired-sample statistics. The colorbar displays the t-values.

In line with previous literature (Shum et al., 2013; Park et al., 2014), the present results show that the visual presentation of single numbers, letters and false fonts elicit a neural response which peaks around 160 ms after the stimulus onset on occipital and occipito-temporal sensors of the MEG. Numbers elicited the largest values in comparison with the rest of the stimuli. Results from the paired-sample t-tests revealed (Fig. 2) significant effects between the conditions over early time-windows ($p < 0.01$, corrected). When comparing with single letters, numbers elicited significant enhanced power over occipito-temporal sensors bilaterally (with higher effect over the right sensors) and over left temporal sensors (124-208 ms). Similarly, when comparing with single false fonts, numbers showed higher power values over left occipito-temporal sensors, over temporal

sensors bilaterally and over central sensors (130-210 ms). When letters were compared with false fonts, the first elicited higher power values over left temporal and central sensors (130-210 ms).

The results of Experiment 1 in the sensors space (Figure 2) showed medium and large effects. Means (M), standard deviations (SD), effect sizes and correlation values of the three conditions (numbers, letters, false-fonts), that result in the significant topographies (sensors) and latencies (tw, time-windows) shown above, are depicted as follows: comparison 1) numbers [$M=.13^{-11}$; $SD=.75^{-12}$] versus letters [$M=.09^{-11}$; $SD=.69^{-12}$], tw: 124-208 ms; effect size: -.54, $r=.91$; comparison 2) numbers [$M=.98^{-12}$; $SD=.57^{-12}$] versus false fonts [$M=.5^{-12}$; $SD=.42^{-12}$], tw: 130-210 ms, effect size: -.95, $r=.84$; comparison 3) letters [$M=.69^{-12}$; $SD=.47^{-12}$] versus false fonts [$M=.32^{-12}$; $SD=.4^{-12}$], tw: 130-210 ms, effect size: -.83, $r=.86$.

Experiment 1. Source space

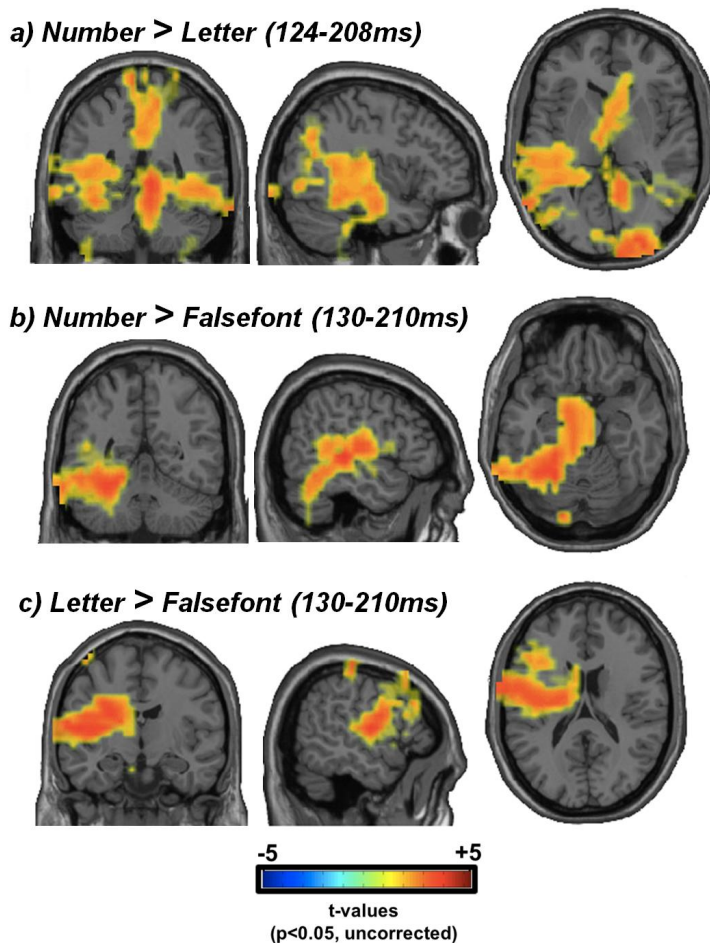


Figure3. Experiment1 sources. Cortical distribution of cluster-based statistical differences in brain activity between the conditions during the significant time-windows found at the sensor space. **Note that only significant effects are shown.**

Contrast	Coordinates [x,y,z]
number > letter	[-3.9, -4.7, 0.3]
number > falsefont	[-5, -5.3, -2]
letter > falsefont	[-5.5, -1.1, 1.7]

Table1. Coordinates of significant sources (MNI). The coordinates of the highest statistical values for each of the contrasts are shown.

Source space analysis was performed over the significant time-windows resulting from the sensor analysis. Paired-sample t-tests were computed between the conditions in order to test for significant differences between the conditions at the source space. In line with the results in sensor space, after selecting the a-priori time-windows of interest, the cluster-based permutation test revealed (Figure 3) a significant difference between the numbers and letters at the source space. These differences were most pronounced over the fusiform gyrus, middle temporal gyrus and auditory cortex of the left hemisphere, and over the inferior temporal gyrus and the secondary visual cortex in the right hemisphere. When testing for effects between numbers and false fonts, the cluster-based permutation test revealed a significant difference which was most pronounced over the fusiform and superior temporal gyrus of the left hemisphere. When testing for effects between letters with false fonts, the cluster-based permutation test revealed a significant difference which was most pronounced over the left inferior prefrontal cortex (and the premotor cortex).

The results of Experiment 1 in the source space (Figure 3) showed medium and large effects. **Means (M), standard deviations (SD), effect sizes and correlation values of the three conditions (numbers, letters, false-fonts), that result in the significant sources at the significant time-windows (tw) in the sensor space are depicted as follows:** comparison 1) numbers [M=2.94; SD=.8] versus letters [M=2.37; SD=.6], tw: 124-208 ms, effect size: -.8, $r=.84$; comparison 2) numbers [M=3.22; SD=.8] versus false fonts [M=2.62; SD=.8], tw: 130-210 ms, effect size: -.74, $r=.35$; comparison 3) letters [M=2.26; SD=.75] versus false fonts [M=1.6; SD=.38], tw: 130-210 ms, effect size: -1.09, $r=.61$.

Experiment 2. Sensor space

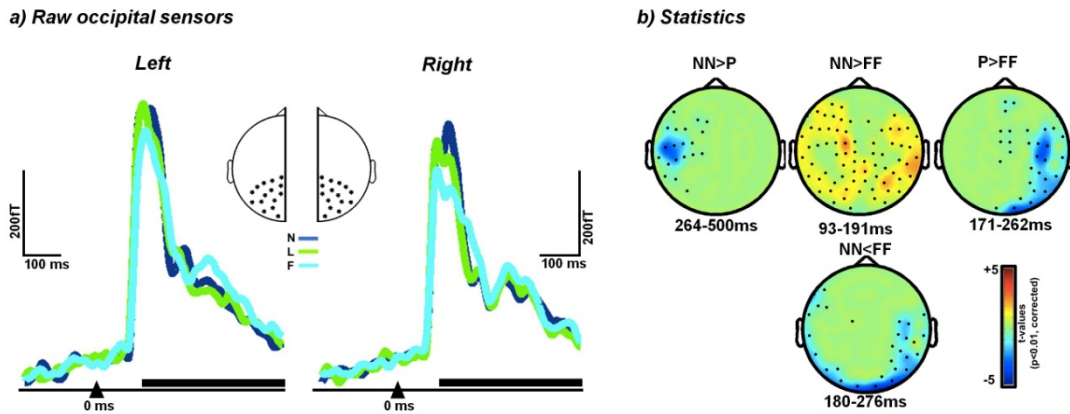


Figure 4. Experiment 2 sensors. a) **Raw occipital sensors.** Raw event related fields (ERF) averaged over the occipital sensors (left and right separately) for visualization purposes (dark blue: strings of numbers; green: pseudowords; light blue: strings of false fonts). The black triangle indicates the stimulus onset (0 ms). The black rectangle indicates the timing of the four significant time windows (264-500 ms, 93-191 ms, 180-276 ms, 171-262 ms) resulting from the t-statistics between the conditions ($p < 0.01$, corrected). b) **Statistics.** Topographies of the distribution of the significant t-statistics at the sensor level (N<P: strings of numbers lower than pseudowords; N>F: strings of numbers greater than strings of false fonts; N<F: strings of numbers lower than strings of false fonts; P>F: pseudowords greater than strings of false fonts). Dark dots display the significant sensors resulting from the paired-sample statistics. The colorbar displays the t-values.

In line with a large previous literature (Park et al., 2012; 2014), the present results show that the visual presentation of number strings, letters strings and false font strings elicit a ERF response which peaks around 160 ms after the stimulus onset occipital and occipito-temporal sensors of the MEG. When testing for effects between the conditions, the paired-sample t-tests revealed (Fig. 3) significant effects between the conditions over early and late time-windows. Number strings elicited a smaller magnitude response than pseudowords during a late time-window (264-500 ms). The cluster was more pronounced over left temporal and frontal sensors. When testing for effects between numbers strings

1 and false font strings, the cluster based permutation test revealed a positive and a negative
2 cluster. During early time-windows (93-191 ms), number strings elicited enhanced power
3 values than false font strings. The cluster was more pronounced over frontal, temporal
4 and occipital sensors of both hemispheres. During later time-windows (180-276 ms), false
5 font strings elicited a larger response than number strings. The cluster was more
6 pronounced over temporal and occipital sensors of both hemispheres. The comparison
7 between pseudowords and false font strings showed a stronger response for false fonts
8 strings during later time-window (171-262 ms). The cluster was more pronounced over
9 temporal and occipital sensors of the right hemisphere.
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17 The results of Experiment 2 in the sensors space (Figure 4) showed medium and
18 large effects. Means (M), standard deviations (SD), effect sizes and correlation values of
19 the three conditions (numbers, letters, false-fonts), that result in the significant
20 topographies (sensors) and latencies (tw, time-windows) shown above, are depicted as
21 follows: comparison 1) numbers [$M=.2^{-12}$; $SD=.34^{-12}$] versus letters [$M=.61^{-12}$; $SD=.49^{-12}$],
22 tw: 264-500 ms, effect size: .96, $r=.75$; comparison 2A) numbers [$M=.015^{-12}$; $SD=.69^{-12}$]
23 versus false fonts [$M=.011^{-12}$; $SD=.5^{-12}$], tw: 93-191, effect size: -.75, $r=.87$;
24 comparison 2B) numbers [$M=.0006^{-12}$; $SD=.1^{-12}$] versus false fonts [$M=.011^{-12}$; $SD=.68^{-12}$],
25 tw: 180-276, effect size: 2.26, $r=.13$; comparison 3) letters [$M=.48^{-12}$; $SD=.33^{-12}$]
26 versus false fonts [$M=.98^{-12}$; $SD=.52^{-12}$], tw: 171-262, effect size: 1.14, $r=.79$.
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Experiment 2. Source space

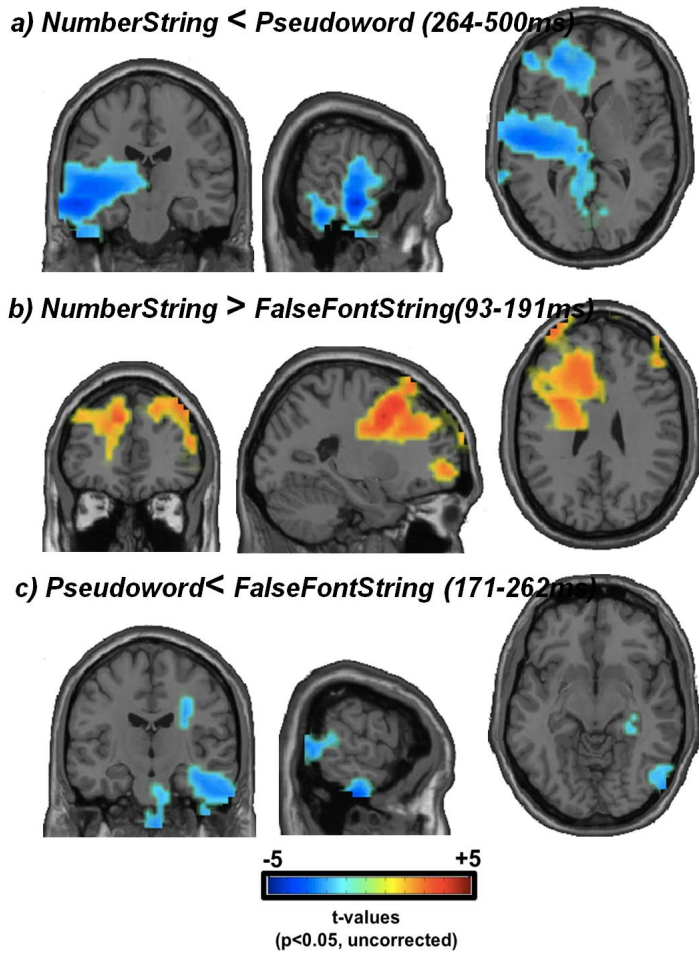


Figure5. Experiment 2 sources. Cortical distribution of cluster-based statistical differences in brain activity between the conditions during the significant time-windows found at the sensor space. **Note that only significant effects are shown.**

Contrast	Coordinates [x,y,z]
numberstring < pseudoword	[-6.1, -2, 0.1]
numberstring > falsefontstring	[-2.4, 4.1, 2.7]
pseudoword < falsefontstring	[6.5, -1.6, -1]

Table2. Coordinates of significant sources (MNI). The coordinates of the highest statistical values for each of the contrasts are shown.

1 Source space analysis was performed over the significant time-windows from the
2 sensor analysis. Paired-sample t-tests were computed between the conditions in order to
3 investigate for significant differences between the conditions. In line with the results in
4 sensor space, after selecting the time-windows already implicated by the sensor analysis,
5 the cluster-based permutation test revealed a significant difference between the number
6 strings and the pseudowords. These differences were most pronounced over the temporal
7 lobe and the DLPFC (dorsolateral prefrontal cortex) of the left hemisphere. When
8 testing for effects between number strings and false font strings, the cluster-based
9 permutation test revealed significant difference which was most pronounced over the
10 DLPFC and premotor of the left hemisphere and over the DLPFC, and inferior frontal
11 gyrus of the right hemisphere. No significant effects were present in source space when
12 testing for the greater response of false font strings, compared with number strings, in
13 source space ($p>0.05$). When comparing pseudowords with false font strings, the cluster-
14 based permutation test revealed a significant effect which was most pronounced over the
15 fusiform, and the temporal lobe of the right hemisphere. No significant effects were
16 evidenced at the source space when testing for higher power values of pseudowords,
17 compared with false font strings, at the source space ($p>0.05$).

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33 The results of Experiment 2 in the source space (Figure 5) showed medium and
34 large effects. Means (M), standard deviations (SD), effect sizes and correlation values of
35 the three conditions (numbers, letters, false-fonts), that result in the significant sources at
36 the significant time-windows (tw) in the sensor space are depicted as follows: comparison
37 1) numbers (M=1.4; SD=.22) versus letters (M=1.82; SD=.44), tw: 264-500, effect size:
38 1.19, $r=.38$; comparison 2) numbers (M=2.76; SD=.57) versus false fonts (M=2.13;
39 SD=.41), tw: 93-191 ms, effect size: -1.24, $r=.54$; comparison 3) letters (M=2.81;
40 SD=.68) versus false fonts (M=3.97; SD=1..43), tw: 171-262 ms, effect size: 1.03, $r=.59$.

41 Discussion

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dissociate preferentially from pseudowords at later time-windows (with the higher differences shown over the left temporal regions, >260 ms) they dissociate from false-font strings in earlier time windows (<200 ms, with the higher differences over the prefrontal and temporal sensors bilaterally). The approach used in the current study, which combines high temporal resolution, a whole-head coverage of the surface of the brain and a source localization of the effects, offers further data about how numbers dissociate from letters and false-fonts. Together, the present data contribute to the notion that the adult human visual system dissociates between these culturally-created symbols at the earliest encoding levels (Park et al., 2015).

Bilateral early preference of numbers. The triple-code-hypothesis (Dehaene, 1995, 1997) postulates that numbers are encoded as strings of digits on an internal visuospatial scratchpad which involve bilateral OT regions of the ventral visual pathway. In support for this, recent evidence shows a preferential response to numbers (compared to physically similar stimuli) over these regions (Park, Hebrank, et al., 2012; Roux et al., 2008). In their iEEG study, Shum et al., (2013) revealed a highly selective response to numerals in the right inferior temporal gyrus, anterior to the occipital temporal incisures. Although most of the electrodes in their patients were implanted in the right hemisphere, they were able to see a similar pattern in the left hemisphere as well. More recently, Groetheer et al., (2016) localized a preferential BOLD response for numbers at the inferior temporal gyrus. Interestingly, this pattern was present in both hemispheres.

This evidence agrees with our current results showing a bilateral preference for single numbers when comparing with letters and false-fonts (Experiment 1). A possible explanation for the bilateral preference during number processing originates from the ‘biased connectivity’ hypothesis. Under this hypothesis, category-specific visual areas emerge at cortical sites that exhibit a higher density of white-matter fiber tracts to and from the cortical circuits that are crucial for the target task. In the case of the *number form area* (NFA) primary target circuits would be the bilateral intraparietal sites that encode non-symbolic numerical quantities (Hannagan et al., 2015). This hypothesis is based on previous data that links connectivity patterns to functional specialization in the symbol form areas. A recent study by Abboud et al., (2015) reveals high connectivity patterns between the NFA and regions involved in representing quantities such as the intraparietal sulcus (IPS). The IPS is involved in the supramodal representation of numbers and is activated bilaterally more strongly when processing numbers than when processing letters

1 (Eger et al., 2003) or false-fonts (Woodhead et al., 2011). Together, the bilateral occipito-
2 temporal preference during number processing could represent a low-level visual
3 processing which drives (via structural and/or functional connectivity) the preferred
4 activation to the higher order areas.
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8 Importantly, the effects in Experiment 1 (single stimuli) showed a peak at early latencies
9 of the visual encoding (between 124 ms and 210 ms). This time-window could be
10 explained by the so-called N1 event-related potential component which is related with the
11 visual encoding and discrimination of visual categories (Rossion, Joyce, Cottrell, & Tarr,
12 2003; Tanaka, Luu, Weisbrod, & Kiefer, 1999). Supporting our results, Dehaene (1996)
13 showed that participants elicited more bilateral N1 activity when engaged in a numerical
14 than in a verbal task.
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22 Together with our results, the most pronounced discrimination (or perceptual
23 specialization) of single numbers, letters forms and false-fonts took place over occipito-
24 temporal regions at the earliest stages of the visual encoding level.
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28 Our data also showed that the dissociation between number strings and false-fonts took
29 place bilaterally early in the visual encoding (93-191 ms) (Experiment 2). Interestingly,
30 the dissociation was more pronounced over the PFC bilaterally (temporal, parietal and
31 occipital sensors were also highlighted). The PFC is involved in semantic association, as
32 shown by Diester et and Niedel (2007). In their study, they trained monkeys to assign
33 visual shapes to numerical categories and recorded from single cells in the prefrontal and
34 parietal regions of the brain. The resulting data showed that the learned numerical value
35 of the visual shapes was encoded by the neurons in the PFC. Furthermore, the data
36 allowed them to propose this region as a neuronal precursor for number symbol encoding.
37 Consistent with this evidence, the greater recruitment of bilateral PFC regions for
38 number-strings may represent the semantic nature of these culturally-learned symbols in
39 comparison with the meaningless symbols. In addition, similarly to previous literature on
40 word processing (Wheat et al., 2010; Woodhead et al., 2012), the current findings could
41 suggest top-down effects from the inferior frontal gyrus to the ventral occipito-temporal
42 cortex during number-string processing.
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55 Contrary to the bilateral preference for numbers, previous literature has shown a right
56 lateralization of the brain activity when processing these symbols. In an EEG
57 investigation, Park et al., (2014) reported a double dissociation when comparing single
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1 stimuli. While numbers activated right sensors more than letters, letters activated left
2 sensors more than numbers. The discrepancy between the studies could be caused by the
3 different methodological approaches used in the analyses. While we used a cluster-based
4 permutation test taking all the sensors into account, Park and collaborators restricted their
5 analysis to two preselected temporal-occipital channels. However, similar to our data, the
6 topography of the raw data in their study evidences a bilateral pattern for numbers. In a
7 similar manner, Carreiras et al. (2015) observed higher ERP responses to number strings
8 over right occipito-temporal regions when comparing with consonant strings. In addition
9 to the different methodological approaches used, the nature of the stimuli could also
10 explain the discrepancies between studies. In a fMRI study, Abboud et al. (2015) used a
11 complex numerosity task and showed a preferential activation for number identification
12 in the right inferior temporal gyrus. However, the uncorrected results also revealed
13 activation of the homologous left gyrus which suggested a possible role of this
14 hemisphere on the identification of numerosity. As mentioned before, the neural response
15 to numbers has been difficult to identify with fMRI due to a high rate of signal loss in this
16 area. To compensate for that, the authors excluded the voxels with the lowest signal
17 strength. This procedure may have hindered bilateral effects and contribute to the
18 discrepancies between studies. Future studies which combine high temporal and spatial
19 resolution techniques together with whole-brain methodological approaches will help to
20 clarify these discrepancies.

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37 *Left hemispheric preference for letters and pseudowords.* According to previous
38 literature (Dehaene, 1995; Polk et al., 2002; Reinke et al., 2008; Vartiainen et al., 2011;
39 Price, 2012), our data (Experiment 1) show left lateralized preference for single letters
40 over the left inferior PFC during the first encoding levels (130-210 ms), when comparing
41 with single false fonts.

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46 As part of the language-processing network, the left inferior prefrontal gyrus is
47 implicated, through a top-down processing to the ventral occipito-temporal cortex, in the
48 integration of general visual form recognition, especially in the processing of visual word
49 forms, (Cai et al., 2010; Wheat et al., 2010; Woodhead et al., 2012). Supported by the
50 connectivity biased between the left temporal cortex and the left inferior frontal gyrus
51 hypothesis (mentioned earlier), the current results could indicate preferential feedback
52 mechanisms between these two regions when processing letter forms. Further studies
53 which include connectivity measures will evaluate such a hypothesis.

1 As far as we are aware of, the preferential response of the inferior PFC to letters or
2 pseudowords (in comparison with false-fonts and numbers, respectively) is a novel result.
3 One of the main reasons of its novelty could be that previous investigations focused their
4 analyses only on the posterior regions of the brain. For example, Park et al., (2012)
5 restricted their analysis to parietal, occipital and temporal regions of interest (ROI) and
6 include only strings of stimuli. Park et al., (2014) restricted their analysis to the posterior
7 sensors which showed the largest effects, as described before. Groetheer et al., (2016)
8 established regions of interest on the right and left number form areas (covering mainly
9 the inferior temporal gyrus), and the iEEG study by Shum et al., (2013) was restricted to
10 the location of the intracranial electrodes (which covered mostly right temporal and only
11 some left temporal regions). However, similar to our results, Carreiras et al., (2015) did
12 observe higher ERF amplitudes in the inferior PFC when processing pseudowords than
13 when processing consonant strings, suggesting a higher activation of this region for
14 higher-pronounceable characters than for less-pronounceable characters. Interestingly,
15 the Z-scores shown in their results suggest a potentially preferential neural response for
16 pseudowords over the left hemisphere when comparing with strings of numbers (as shown
17 in our study).

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34 In the Experiment 2, pseudowords elicited a left lateralized preference when compared
35 with number strings. Interestingly, this dissociation emerged in later time-windows (264-
36 500 ms) and showed the largest effect over the left temporal cortex, including the fusiform
37 gyrus, and the left inferior PFC. The left inferior temporal cortex is shown to be sensitive
38 to visual word forms (McCandliss et al., 2003). Furthermore, the preferential recruitment
39 of the left fusiform and temporal gyri during word form processing is a robust finding in
40 the literature (Cohen et al., 2002; Binder et al., 2006; Baker et al., 2007;) and is consistent
41 across orthographies (Dehaene and Cohen, 2011). Park et al., (2012, 2014) have recently
42 investigated with fMRI and EEG how the brain dissociates between letters and numbers.
43 Similar to our results, their participants also recruited the left fusiform and inferior
44 temporal gyri more when processing letters than when processing numbers.

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55 Importantly, the dissociation between pseudowords and number strings in our study was
56 more prominent starting approximately 264 ms. This time-window is coincident with the
57 so-called P2 event-related potential component. This ERP component is a positive
58 deflection starting approximately 250 ms after stimulus onset and is modulated by the
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linguistic aspects of the stimuli, such as phonology and semantics (Barber et al., 2004, Carreiras et al., 2005; Hauk et al., 2006). During lexical decision tasks, pseudowords elicit larger amplitude responses than words in the P2 component (Hauk et al., 2006). During semantic tasks, words elicit larger amplitudes than consonant strings (McCandliss et al., 1997). Based on this, our results showing a difference in the amplitude between 264-500 ms between pseudowords and number strings but not between single letters and numbers could suggest that the visual cortex may be implicitly extracting phonological or semantic information when processing word-like stimuli. Park et al., (2014) obtained a similar pattern of results and elegantly suggested that such results could be explained by a later stage of a hierarchy of local combination detectors (Dehaene et al., 2005). Under this hypothesis, combinations of characters (such as pseudowords) may be processed more effectively by neurons in the higher levels of the visual-word-form processing, while neurons in the lower levels may process single characters. Such a hypothesis should be addressed in future investigations.

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Right occipito-temporal preference for false-fonts. It is noteworthy to mention that false-font strings preferentially recruited right occipito-temporal regions between 171-262 ms when comparing with pseudowords (Experiment 2). At a first glance, these results might seem somewhat unexpected. However, enhanced activity to non-nameable stimuli such as pseudowords has been previously observed (Park et al., 2014; Park, Hebrank, et al., 2012; Vinckier et al., 2007) over regions of the right hemisphere (Beason-Held et al., 1998; Haxby et al., 1995).

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As mentioned earlier, the occipito-temporal region is a brain area sensitive to visual word forms. It is an area where categories, like words, are first identified and where the linguistic aspects of the stimuli commence after to be extracted. This pattern of activity seems to suggest that unfamiliar objects require more processing for identification and categorization (Appelbaum et al., 2009; Herdman, 2011; Herdman and Takai, 2013). Potentially, the localization and latency of the effects could potentially show an inefficient (and implicit) extraction of phonological or semantic information from the unknown stimuli. On a similar view and consistent with the study by Park, et al. (2012) in which they observed a larger fMRI response to false fonts than to letters in a study of monozygotic twins, the current results could be explained by an inefficiency in the template-matching process for unfamiliar stimuli that propagates through later phases of the processing.

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Conclusion. The results obtained in the current study suggest that the visual cortex (and importantly also prefrontal regions) discriminates between numbers, letters and false- fonts at early stages of the visual encoding. Our data show the importance of combining high temporal and spatial resolution techniques in order to fully understand the mechanisms underlying such dissociation. Together with previous evidence, our data point towards a new example of acquired category-specific responses in the human visual system. Future investigations will evaluate the current results and will contribute to the knowledge on how experience tunes the visual system for category recognition.

Data availability statement

The data generated during the current study are publicly archived at the following URL:
<https://openneuro.org/datasets/ds001985/versions/1.0.0>

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