

## Numbers are not like words: Different pathways for literacy and numeracy

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## Abstract

Literacy and numeracy are two fundamental cognitive skills that require mastering culturally-invented symbolic systems for representing spoken language and quantities. How numbers and words are processed in the human brain and their temporal dynamics remain unclear. Using MEG (magnetoencephalography), we find brain activation differences for literacy and numeracy from early stages of processing in temporal-occipital and temporal-parietal regions. Native speakers of Spanish were exposed to visually presented words, pseudowords, strings of numbers, strings of letters and strings of symbols while engaged in a go/no-go task. Results showed more evoked neuromagnetic activity for words and pseudowords compared to symbols at ~120-130 ms in left occipito-temporal and temporal-parietal cortex (angular gyrus and intra-parietal sulcus) and at ~200 ms in left inferior frontal gyrus and left temporal areas. In contrast, numbers showed more activation than symbols at similar time windows in homologous regions of the right hemisphere: occipito-temporal and superior and middle temporal cortex at ~100-130 ms. A direct comparison between the responses to words and numbers confirmed this distinct lateralization for the two stimulus types. These results suggest that literacy and numeracy follow distinct processing streams through the left and right hemispheres, respectively, and that temporal-parietal and occipito-temporal regions may interact during processing alphanumeric stimuli.

## Introduction

The ability to use and manipulate both words and numbers is essential in a knowledge-based society. It remains unclear, however, how these objects are visually processed in the brain. Different processing pathways have been hypothesized for words and numbers from the observation of dissociated impairments in brain-lesioned patients (Anderson et al., 1990), although the extant evidence remains inconclusive (Starrfelt and Behrmann, 2011, see also McCloskey & Schubert, 2014).

An increasing body of research has highlighted the role of the left fusiform gyrus in visual word processing (Dehaene and Cohen, 2011). This region responds more to real words and pseudowords than consonant strings or false fonts (Baker et al., 2007; Binder et al., 2006; Cohen et al., 2002; Reinke et al., 2008). Nevertheless, *how* and *when* such information is computed in this area remains controversial (Carreiras et al., 2014; Price and Devlin, 2003, 2011).

Consistent with the hypothesis that number recognition is dissociable from letter recognition, studies using intracranial electrophysiological recordings report number-specific responses in different brain regions (Allison et al., 1994; Roux et al., 2008; Shum et al., 2013). Many fMRI studies, however, report more activation to words than digits in the left fusiform but do not identify areas that respond more to digits than alphabetic stimuli (Baker et al., 2007; Polk et al., 2002; Price and Ansari, 2011; Reinke et al., 2008). There are a few notable exceptions. Stronger activation for number processing than letter processing has been found bilaterally in the horizontal intra-parietal sulcus (Eger et al., 2003), and more recently, a double dissociation between letter and number visual recognition has been reported (Park et al., 2012). In particular, strings of consonants activated the left mid-fusiform and inferior temporal gyri more than numbers, whereas strings of numbers activated right lateral occipital

areas more than letters. Recently, Carreiras et al., (2014) showed that the left fusiform and left superior and inferior parietal regions were activated more for letters than digits. Meanwhile, right superior parietal regions were activated more for digits than letters, suggesting that processing may follow distinct pathways. Still, the lateralization of number stimuli is unclear because numeric-specific responses have been identified in both hemispheres using fMRI and intracranial recordings (Shum et al., 2013). Moreover, only one recent study using EEG (Park et al., 2014) has addressed *when* this dissociation might occur. In two experiments, they found an early divergence between ERP traces to letters and numbers. In particular, letters elicited significantly larger N1 amplitudes than numbers in left electrodes, while numbers elicited significantly larger N1 amplitudes than letters in right electrodes.

While the activation of the left fusiform to words and pseudowords is consistent across orthographies (Dehaene and Cohen, 2011), a preferential brain response for numbers has yet to be established since the primary evidence comes from a) brain lesions, which can be variable, b) intracranial recordings, which are restricted spatially to where the grids can be placed, and c) previous negative fMRI findings that could arise from the limited temporal resolution of the BOLD response in capturing extremely fast processes. Furthermore, it is possible that common neural generators are recruited given the similar scalp topographies found for words and numbers in Park et al., (2014), despite the fact that the difference-wave topographies revealed focal differentiation in occipital sites for the two types of stimuli. In addition, fast feedback processes from anterior to occipito-temporal areas during visual word recognition have been found previously using MEG (Wheat et al., 2010; Woodhead et al., 2012). Thus, this dissociation between letters and numbers may not be restricted to just occipital sites but may rapidly propagate to other brain areas, such as temporal-

parietal areas previously reported with fMRI (Carreiras et al., 2014). Here, we use MEG, a technique that combines high temporal precision with good spatial resolution, to investigate the underlying brain circuits and temporal dynamics of words and numbers, i.e., the *when* and *where* of word and number processing.

## **Materials and Methods**

**Participants:** Sixteen right-handed (as assessed by the Edinburgh handedness survey (Oldfield 1967)) native Spanish speakers (9 female; age range: 19-37 years; mean: 25 years (SD: 5.4)) voluntarily participated in the current MEG study. All had normal or corrected to normal vision and did not report any neurological deficits. All participants provided written informed consent in accordance with guidelines approved by the Research Committees at the Basque Center on Cognition, Brain and Language.

**Stimuli:** A set of 75 words, 75 pseudowords, 75 numbers, 75 consonant strings and 75 symbol strings were selected. The 75 words (e.g., “ERROR”) were 4 or 5-letters long ( $M=4.53$ ;  $SD=0.50$ ), had a mean frequency of 23.58 ( $SD=23.49$ ) appearances per million words and had an average number of 7.16 orthographic neighbors ( $SD = 5.32$ ; Davis and Perea, 2005). All words were carefully selected so that only nine distinct letters were used in the entire set: The three vowels A, E and O, and six consonants C, S, R, L, T and N. The 75 pseudowords were created by replacing vowels from the word set (e.g., the pseudo-word “ORRAR” from the word “ERROR”). Words and pseudowords were matched in a pairwise manner for their mean bigram frequencies ( $p>.34$  for the token bigram frequency and  $p>.10$  for the

type bigram frequency; Davis and Perea, 2005). The 75 number strings were created by replacing each of the letters from the word set for a given number (e.g., “83393”; 1 for C, 2 for S, 3 for R, 4 for L, 5 for T, 6 for N, 7 for A, 8 for E and 9 for O). The 75 consonant strings contained only consonants in the word and pseudoword conditions (namely, C, S, R, L, T and N). The length of these strings was identical to that of the other sets (e.g., “LTRNC”). The 75 symbols strings were created by replacing each of the letters from the word set for a symbol (e.g., “@&&>&”; \$ for C, % for S, & for R, € for L, ? for T, ! for N, + for A, @ for E and > for O). In the end, we created a set of 375 trials (75 items per group of stimuli). These were the no-go trials of a go/no-go task in which participants were asked to respond to go trials that contained a □ inserted into the string. Seventy-five go trials were created by reconfiguring the different characters of the previously defined types of strings and including a dot within the string at different positions, counterbalancing both the type of characters and the location of the dot (e.g., “86·39”, “EC·SA”), resulting in a 5-to-1 ratio of no-go to go trials.

**Procedure:** Prior to recording each participant, we digitized the positions of three landmarks (nasion and pre-auricular points) and four head-position indicator (HPI) coils placed on the high forehead and above the ears. We also digitized the participant’s head shape to improve the co-registration accuracy between MEG and individual structural MRIs. During the MEG recordings, participants sat in the magnetically shielded room on a comfortable chair with their head in the MEG sensor helmet.

Stimuli were presented one at a time in the center of a screen (white letters on a dark grey background; no word exceeded a visual angle of about 3°). Stimulus

presentation began with a 500 ms fixation point (“\*”), immediately followed by target stimulus, which was also displayed for 500 ms. Participants were instructed to respond whether a dot was presented as part of a stimulus by pushing a button and withhold the response if no dot was present in the stimulus. Trial order was randomized for each participant, and the inter-trial interval (ITI) pseudo-randomly varied between 900 to 1200 ms. The experiment was divided into three blocks separated by two breaks. Participants were asked to avoid movements, blinks and other eye movements during the presentation of each item. To ensure their understanding of the instructions, participants were first presented with 20 practice trials under the experimenter’s observation. Prior to the start of the experiment, HPI coil positions were determined with respect to the MEG sensors. If the HPI inter-coil distances differed by more than 4 mm from those obtained with the digitizer, the digitization procedure was re-run. Head tracking was employed throughout the experiment. Each experimental session lasted less than 20 minutes.

**Data acquisition:** Participants were seated in a dimly lit magnetically shielded room while stimulus-evoked neuromagnetic activity was recorded using a whole-head 306-channel Vectorview system (Elekta Oy, Helsinki, Finland), which utilizes both planar gradiometer and magnetometer SQUID sensors. The MEG signal was recorded at a 1 kHz sampling rate and a band pass filter with frequency cut-offs at 0.1 Hz and 330 Hz applied during data acquisition. To carry out the minimum L2-norm estimations, a high-resolution 3D structural MR image (T1-weighted MPRAGE sequence) was acquired with a 3T Trio scanner (Siemens, Munich, Germany) for each participant.

**Data processing:** Continuous MEG data were pre-processed off-line using the signal-space separation method, which suppresses external interference and corrects for head movements (Taulu et al., 2005). We then extracted 850 ms epochs (including 200 ms pre-stimulus baseline, zero point at stimulus-onset) from the continuous MEG signal for each participant for each condition. Epochs with EOG signal variation exceeding 150  $\mu$ V, MEG magnetometer variation exceeding 3000 fT, or MEG gradiometer variation exceeding 2000 fT/cm were excluded from subsequent analyses (16% of total trials; no difference across conditions). Finally, the remaining epochs were visually inspected for noisy responses. In two participants, we detected dipolar patterns due to residual ocular activity. This activity was consequently modeled with an equivalent current dipole (ECD) and projected out from the data.

**Source analyses, MNE:** Cortically-constrained minimum L2-norm estimates with thousands of candidate sources (dipoles) distributed over the cortex were calculated using the MNE software (version 2.7, M. Hämäläinen, Athinoula A. Martinos Center for Biomedical Imaging, Boston, USA).

The geometry of the cortical surface and cranial volume of each participant was extracted from individual MR images using the FreeSurfer software (Dale and Sereno, 1993; Fischl et al., 1999). Reconstructed cortical surfaces were decimated to 5120 potential source locations per hemisphere, corresponding to  $\sim 5$  mm distance between neighboring source points. The head position index (HPI) measurement, the location of the three fiducial landmarks and the scalp points (at least 100 points per participant) were used to align the source spaces and the single-compartment boundary element model (BEM) of the head conductivity with respect to the MEG sensors.

Currents along the normal direction of the local cortical surface were favored over the transverse direction by applying a loose orientation constraint of 0.3 (Lin et al., 2006). In addition, using a depth-weighting exponent of 0.4 reduced the inherent bias of minimum-norm estimates toward superficial currents. A common noise-covariance matrix across all conditions was estimated from the 200 ms segments of the unaveraged data preceding the stimulus.

We then calculated the noise-normalized MNE (i.e., dynamical Statistical Parametric Mapping (dSPM); Dale et al., 2000) from 0 to 650 ms post-stimulus onset. We employed the estimation of the sensor-level evoked activity for source reconstruction. Prior to MNE estimation, sensor-level evoked activity was low-pass filtered at 40 Hz with a 10 Hz filter width, and the data were down-sampled to 500 Hz. Individual MNE solutions were morphed to an average cortical model (calculated by FreeSurfer based on the cortical surfaces of our 16 participants). This average cortical surface was used to average normalized (z-scores) MNEs across participants.

To statistically evaluate the main effects of interest, we contrasted the noise-normalized solutions within specific regions of interest (ROI) derived from a parcellation of the cortical surface implemented in FreeSurfer (Destrieux et al., 2010). We opted for the ROI strategy of analysis to better connect our results with previous findings. MNE source reconstruction does not permit a high enough spatial resolution to identify more fine-grained localizations of regions underlying the sensor-level effect. Possible leakage from the real source of an effect to neighboring regions could overestimate a given brain region's activation by a specific stimulus category. As such, we reasoned that our approach is more conservative by testing the present data against previous findings. Based on prior MEG reports of visual word processing (Pylkkänen et al., 2002; Vartiainen et al., 2011), we focused on homologous regions in

both hemispheres. The identified ROIs and their anticipated temporal-profiles of activation are as follows. The *occipital pole* is involved in the initial visual analysis of printed stimuli (Dale et al., 2000). Then, increased activity around 150-170 ms in the lateral *occipital-temporal regions* of the scalp is expected (*fusiform gyrus*). These regions are purportedly involved in the visual-orthographic processing of the stimulus (Thesen et al., 2012). Evoked activity is then hypothesized to spread to temporal regions of the scalp at around 350-400 ms (Salmelin, 2010). Such regions are involved in the lexical/semantic analysis of stimulus (Dale et al., 2000; Friederici et al., 2003; Lau et al., 2008). We thus included in our ROI analysis the *middle temporal gyrus*, the *superior temporal gyrus* and the *superior temporal sulcus*. Given the size of these regions, the *middle temporal gyrus* and the *superior temporal sulcus* were divided into three sub-regions (see Molinaro et al., 2013): Anterior (MNI coordinates in the y axis from 7.5 to -20 on average), Medial (from -20 to -40) and Posterior (from -40 to -60). The *superior temporal gyrus* was divided into two subregions: Anterior and Posterior, with respect to the -20 y axis value. Furthermore, we included the *inferior frontal gyrus* (*pars opercularis*, *triangularis* and *orbitalis*) and the more posterior perisylvian *subcentral gyrus* that has recently been suggested to play a critical role in the initial stages of visual word recognition (Wheat et al., 2010; Woodhead et al., 2012). To control for possible effects due to motor-related activity (e.g., suppression of motor response), the *precentral gyrus*, *central sulcus* and *postcentral gyrus* were included in the analysis. Finally, because our study focused on the comparison between letter and number neural processing correlates, we included two additional bilateral parietal regions implicated in numerical cognition (Dehaene et al., 2003), i.e., the *angular gyrus* and the *intra-parietal sulcus*. The described ROIs

are represented in Figure 1 across different views of the left hemisphere. The homologous right hemisphere regions were also analyzed.

-- please insert Figure 1 around here --

We focused on the dSPM values, i.e, noise-corrected z-scores (for each single participant) in which noise was estimated from the pre-stimulus -200–0 ms time interval, averaged across all conditions. This transformation reduces inter-individual variability in the source level effects. We extracted the time course of activity within each region, spatially averaging the absolute dSPM values across the covered source dipoles for each participant and condition. We report the resulting values on the brain surfaces in Figures 2-7 for each experimental condition.

Subsequently, we applied permutation tests to identify the time intervals in each ROI that showed significant experimental contrasts (consonant strings vs. symbols; numbers vs. symbols; pseudowords vs. symbols; words vs. symbols). Symbol strings were selected as the baseline, since symbols are approximately as familiar as stimuli in the other experimental conditions, while preserving comparable visual complexity. A similar set of analyses was carried out using letter strings as the baseline. This analysis provided similar results, although letter strings produced more left lateralized activation. As such, only the symbol baseline analysis is reported here. Finally, we directly compared the word and number conditions. The contrast was tested in both directions: words > numbers and numbers < words. This was done to shed light on the question of the potential specialization of the different neural pathways involved in number versus word processing.

We employed a non-parametric test that does not require assumptions about the correlation structure of the data and provides corrected p-values for any number of subjects, time points and recording regions (Blair and Karniski, 1993; Galan et al., 1997). This procedure enabled us to determine the location and timing (i.e., ROIs and intervals of interest, respectively) in which experimental contrasts showed significant differences. The method generates surrogate data sets by randomly permuting the condition labels and computing a t-test for each permuted data set. For each set, the maximum t-value across regions and time points is kept for determining the empirical distribution and effectively handling the problem of multiple comparisons. The global null hypothesis of equal means between groups in each region and time point is rejected if the t-statistic obtained from the original (non-permuted) data set is lower or higher than the 2.5 and 97.5 percentiles of the empirical distribution of the maximum, respectively. This procedure effectively controls the family-wise error (FWE) and properly deals with the multiple comparison problem (Lage-Castellanos et al., 2010). To obtain robust timing of the effects in each ROI, only regions showing scores significantly different from the noise level (z-score > 2.2 corresponding to  $p = 0.01$ ) were considered in the analysis. We report and interpret only statistically significant time points ( $p < 0.01$ ) that form a contiguous time window of at least 20 ms in duration.

## RESULTS

**Behavioral:** Accuracy in the go/no-go task was at ceiling (99.47% mean accuracy; SD: 0.98%; range: 97.33% - 100%), indicating that participants attended to

the stimuli during the experiment. Furthermore, the total number of false alarms (i.e., responses to no-go trials) was very low (11 across all participants), with no participant making more than three false alarms.

**Source analyses, MNE.** Source analyses for all conditions revealed the earliest peak of activity in the occipital poles (~100 ms). Lateral occipital-temporal and posterior temporal regions showed subsequent uni-/bi-lateral activity (~150 ms). In these regions, magnetic activity revealed modulations depending on the type of stimulus: words, pseudowords and consonant strings displayed increased activity in the left hemisphere, while numbers displayed an additional increase in activity in the right hemisphere (all compared to the control “symbols” conditions that did not show reliable effects; see Figures 2 and 3). Neuromagnetic activity in bilateral temporal regions did not elicit any clear peak, but showed sustained effects from around 200 ms to 600 ms post-stimulus onset. Among the three temporal regions of interest, activity was larger in the superior temporal sulcus compared to the superior and middle temporal gyrus. Importantly, parietal regions showed increased activity starting just after 100 ms, while inferior frontal regions showed increasing activity starting at 200 ms (see Figures 4-7). In the following sections, we detail the differential neuromagnetic activity recorded for the experimental conditions (consonant strings, numbers, pseudowords and words) compared to the control condition (symbols) and finally, provide the direct contrasts between words and numbers.

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*Consonant strings vs. Symbols.* Differential activity between these two conditions resulted in a few sparse effects in the left hemisphere (Supplementary Figure 1): precentral gyrus (146–188 ms), intraparietal sulcus (186–222 ms) and *pars opercularis* (612–648 ms).

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*Numbers vs. Symbols.* The numbers condition compared to symbols elicited reliable differential activity involving regions of the right hemisphere. Specifically, the earliest effect emerged in right occipital and occipital-temporal regions (see Figure 3). In the occipital pole, numbers elicited increased activity between 62 and 126 ms, while in right fusiform regions, the effect emerged between 104 and 150 ms (but also 584–614 ms).

Additional right hemisphere regions showed increased activity for numbers (see Figure 4 and Supplementary Figure 2). In the right temporal lobe, additional early activation ~120 ms was observed in posterior portions of each region: in the middle temporal gyrus (posterior portion: 120–172 ms, 296–400 ms, 460–648 ms; medial portion: 142–168 ms, 184–222 ms) and in the superior temporal sulcus (posterior portion: 112–154 ms, 558–636 ms; medial portion: 130–156 ms, 194–222 ms). Later, right temporal effects were observed in the superior temporal gyrus (posterior portion: 202–242 ms; anterior portion: 222–290 ms, 526–568 ms) and in the anterior portion of the middle temporal gyrus (370–422 ms, 520–648 ms). The effects observed in the right postcentral gyrus (192–248 ms) and in the right central sulcus (114–156 ms, 198–238 ms) present the same temporal profiles of the effects observed in temporal regions, which potentially reflects some leakage from those regions. A left-hemisphere effect was observed in the intraparietal sulcus between 158 and 198 ms.

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*Pseudowords vs. Symbols.* This contrast elicited the largest differential activity in the left hemisphere. The earliest effects were evident in left posterior occipital, occipital-temporal and parietal regions. In the occipital pole, pseudowords elicited increased activity between 124 and 146 ms, while in the fusiform, the difference was statistically reliable between 126 and 156 ms (Figure 3). In left parietal regions (Figure 5, Supplementary Figure 3), the effect had a similar time course (intraparietal sulcus: 132–160 ms; angular gyrus: 130–160 ms). An early differential effect was also evident in the posterior portion of the superior temporal sulcus (122–154 ms) and in the left central sulcus (132–196 ms, again, potentially reflecting leakage from parietal regions).

Left temporal and frontal regions showed increased activation for pseudowords in later time windows (Figure 5, Supplementary Figure 3). In temporal regions, the effect was significant in the middle temporal gyrus (medial portion: 280–306 ms, 324–400 ms; anterior portion: 248–294 ms, 364–398 ms, 614–648 ms), superior temporal sulcus (medial portion: 216–246 ms, 286–332 ms, 338–444 ms; anterior portion: 220–290 ms, 350–540 ms, 574–648 ms), and superior temporal gyrus (posterior portion: 384–414 ms; anterior portion: 228–290 ms, 358–386 ms, 572–648 ms). In inferior frontal regions, the effect was significant in the *pars opercularis* (212–268 ms, 404–558 ms, 574–648 ms), *pars triangularis* (240–282 ms, 306–352 ms) and *pars orbitalis* (202–368 ms). The effect was also significant in the subcentral gyrus (356–648 ms).

-- please insert Figure 5 around here --

*Words vs. Symbols.* Differential activity for this contrast reliably emerged in left occipital-temporal regions and left temporal regions. In the left occipital-temporal regions, words elicited increased activity compared to symbols in the time-window between 80 and 110 ms (and also 126–154 ms) in the occipital pole and between 124 and 150 ms (and also 204–230 ms) in the fusiform region (Figure 3). A similarly early effect was also evident in the posterior portion of the middle temporal gyrus (118–148 ms, Supplementary Figure 4).

In later time windows, increased activity for words (compared to symbols) was statistically reliable in left temporal and frontal regions (Figure 6, Supplementary Figure 4). In temporal regions, statistically reliable effects were observed in the anterior portion of the middle temporal gyrus (210–284 ms), in the superior temporal sulcus (medial portion: 396–426 ms; anterior portion: 206–304 ms) and in the anterior portion of the superior temporal gyrus (210–300 ms; 610–648 ms). Inferior frontal effects were observed in the subcentral gyrus (364–452 ms, 622–648 ms), *pars opercularis* (236–272 ms, 374–446 ms, 526–648 ms) and *pars orbitalis* (590–648 ms).

-- please insert Figure 6 around here --

*Words vs. Numbers.* Available findings point toward a hemispheric dissociation between linguistic and numerical stimuli (see above). Consequently, we directly compared Numbers and Words to test this observation. In Figure 7, we report the observed activation increases for words compared to numbers in the left hemisphere and numbers compared to words in the right hemisphere.

Words elicited increased activity in the left occipital pole in both an early (130–272 ms) and late time interval (414–456 ms). Later, words elicited increased

activity in the left superior temporal gyrus (posterior portion: 334–456 ms, 480–520 ms; anterior portion: 246–648 ms), the left superior temporal sulcus (posterior portion: 420–452 ms; medial portion: 322–450 ms, 506–544 ms; anterior portion: 252–374 ms, 408–440 ms, 502–560 ms) and in the left middle temporal gyrus (medial portion: 412–444 ms; anterior portion: 252–364 ms, 550–592 ms). In left inferior frontal regions, words elicited more activity than number in the *pars opercularis* (358–648 ms), the *pars triangularis* (574–648 ms) and the *pars orbitalis* (296–342 ms, 466–506 ms, 464–648 ms).

Numbers elicited larger increase of activity compared to words in the right hemisphere. An early effect was evident in the right fusiform gyrus (134–156 ms). Increased activity for numbers was also evident in the right temporal regions and specifically, in the superior temporal gyrus (anterior portion: 188–216 ms), the superior temporal sulcus (posterior portion: 132–196 ms, 342–410 ms, 540–626 ms), and the middle temporal gyrus (posterior portion: 318–648 ms; medial portion: 346–402 ms; 516–648 ms). Finally, an additional effect in the same direction was observed in the right occipital pole (494–604 ms).

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**Summary:** Early sensory analyses of the visual input elicited an initial increase of activation in occipital regions. This activity was reliably modulated depending on the stimulus type. Consonant strings did not robustly dissociate from symbols. Statistical analyses showed early and short-lived effects for numbers, words and pseudowords compared to symbols: numbers elicited increased right lateralized

activity around ~60 ms, words triggered left lateralized effects around ~80 ms and pseudowords a left lateralized effect at ~120 ms.

Later, numbers elicited increased right lateralized activity in occipital-temporal (fusiform) regions ~100 ms. Words and pseudowords elicited a left lateralized effect beginning at ~120 ms in occipital-temporal (fusiform) and posterior temporal.

Subsequent right lateralized activity for numbers primarily involved the temporal lobe, originating at ~120 ms. (The only left hemisphere activation was found at ~160 ms in the intraparietal sulcus.) Pseudowords elicited left lateralized effects in parietal (~130 ms), temporal and inferior frontal regions (~220 ms). Slightly similar temporal and inferior frontal effects were observed starting respectively at ~200 and ~230 ms.

Direct comparison between words and numbers demonstrated the predominant left-hemispheric increase of activation for alphabetic stimuli and the right-hemispheric increase of activation for numeric stimuli, as well as early effects in both ventral and dorsal regions.

## **Discussion**

The present results provide strong evidence (1) that literacy and numeracy rely on distinct networks and (2) that not only occipito-temporal (fusiform) regions but also parietal, temporal and a bit later, inferior frontal areas are implicated in the early stages of processing alphanumeric stimuli. While the reading of words and pseudowords is largely left lateralized, the processing of numbers follows a right lateralized pathway, demonstrating a relative degree of neural specialization between word recognition on the one hand and number recognition on the other. Additionally, concurrent activation for words and pseudowords in occipito-temporal (e.g., fusiform)

and temporal and parietal regions (e.g., middle temporal gyrus, left angular gyrus, left intra-parietal sulcus) suggests they may be engaged in concurrent processing.

Greater left hemisphere activation for words/pseudowords than consonant strings and symbols replicates previous results obtained using fMRI and MEG (Baker et al., 2007; Park et al., 2012; Polk et al., 2002; Price, 2012; Reinke et al., 2008; Tarkiainen et al., 1999; Vartiainen et al., 2011). Thus, the present study provides additional empirical evidence for a left lateralized circuit for reading.

More importantly, however, our results suggest that number processing follows a distinct pathway through the right hemisphere. The right lateralized neural circuit for number recognition is a novel finding that extends previous results obtained with fMRI and EEG (e.g., Park et al., 2014; Park et al., 2012). Previous attempts using fMRI have failed to identify a specialization for number processing relative to letter processing (Baker et al., 2007; Polk et al., 2002; Price and Ansari, 2011; Reinke et al., 2008). Moreover, data from patients have shown no clear dissociation in word and number reading, at least not following left posterior lesions, which appear to affect the processing of both stimulus types (Starrfelt and Behrmann, 2011; McCloskey & Schubert, 2014). Furthermore, evidence from intracranial recordings that have shown more responsiveness to numbers than letter strings in inferior temporal gyrus (Allison et al., 1994; Shum et al., 2013) is not conclusive regarding laterality. Only two recent studies have shown right lateralization for number processing (Park et al., 2012; 2014). Consequently, the existing evidence supporting dissociated, lateralized pathways for number versus word processing is scarce, inconsistent and inconclusive. Here, we demonstrate a brain circuit that underlies visual number processing that is right lateralized, including activation in several regions: right occipito-temporal, right middle temporal gyrus, right superior temporal gyrus, right superior temporal sulcus,

right postcentral gyrus, and right central sulcus. This was found using both consonant strings and symbols as the baselines, and more critically, by directly comparing the differential activation patterns for numbers and words. Furthermore, we found increased activation for numbers in the left intraparietal sulcus and have shown that the differentiation in processing pathways begins very early, not only in occipito-temporal but also middle and superior temporal regions.

What might be the source of the different pathways? Words and numbers are strikingly similar in some regards: They are both cultural-specific invented mental objects and are both representational primitives recruited into recursive mental operations, i.e., numbers in mathematical computations and words in human language syntax. Thus, in principle, no differences might be expected in the underlying brain mechanisms. There are two important differences to consider, however, between words and numbers. First, we store specific words (at least 10,000) in long-term memory, i.e., the lexicon. While humans may be able to distinguish the visual representation of numbers from one another like words, we do not likely have a similar list for numeric representations, at least of the same magnitude. Second, words and numbers link to distinct domains of higher order processing, such as language, visuo-spatial processing and number cognition.

The strong left hemisphere asymmetry for language at the population level (Josse and Tzourio-Mazoyer, 2004; Toga and Thompson, 2003) might also bias the left lateralization of visual word recognition. Conversely, the right hemisphere bias for some number processing operations (Cantlon et al., 2006; Cappelletti et al., 2010; Carreiras et al., 2010; Chochon et al., 1999) may bias visual digit processing to the right hemisphere. Some evidence for a relationship between anterior language structures and ventral occipito-temporal activity during reading has been provided

(Cai et al., 2008; Cai et al., 2010). These authors report that reading-related activity in ventral occipito-temporal regions in healthy individuals lateralized to the hemisphere that was dominant for speech and that such results favor lateralization for the ventral occipito-temporal cortex. Moreover, they suggest that activation for printed words may result from top-down effects from inferior frontal areas due to the integration of general visual form recognition processes within the language-processing network (Cai et al., 2010). Thus, the lateralization of the visual word recognition system may be a function of the interaction with other word processing structures. Interestingly, recent evidence strongly points toward top-down effects from the inferior frontal gyrus to the ventral occipito-temporal cortex during visual word processing (Wheat et al., 2010; Woodhead et al., 2012). The current data also show early activation of the left inferior frontal gyrus but does not support feedback mechanisms, since activation in the inferior occipito-temporal cortex occurs in an earlier time window. In contrast, feedback mechanisms from left parietal (e.g., angular gyrus and left intra-parietal sulcus) to occipito-temporal areas may be at work, as the activation of these three regions overlap in time. Interestingly, the activation of left parietal regions, including the left angular gyrus, was found for orthographic processing (Carreiras et al., 2014). This is a novel finding that is consistent with idea of the angular gyrus playing a modulatory role on occipital cortical activity (Carreiras et al., 2009) and that there are several functional pathways in the reading circuit that originate in occipital cortex that obviate the left fusiform (Richardson et al., 2011). Ultimately, these findings provide a neurobiological platform for investigating top-down effects in the dorsal pathway and thus offer interesting avenues for future research. It should be noted that the inability to observe consistent results in the literature likely stems from the utilization of distinct tasks across experiments and that the amount of observed feedback may be

modulated by task demands. The task in the current experiment did not emphasize higher-order processing of the stimuli on the part of the participant. Consequently, tasks more likely to engage semantic processing and networks might also be more likely to emphasize feedback mechanisms.

While printed words belong to the domain of language, number cognition has its own circuit. The link between visuo-spatial attention and number processing can contribute to this right lateralization bias. One of the most influential models of number processing, i.e., the “triple-code model”, assumes three distinct systems of representation, one of which is a visual system responsible for coding numbers as Arabic numerals (Dehaene et al., 2003) that is subserved by a posterior superior parietal system strongly engaged in spatial visual attention processes. This link can contribute to the right lateralized pathway for visual number processing, since it has been shown that the left lateralization of language and the right lateralization of spatial attention are dependent with an evolutionary origin (Cai et al., 2013). Furthermore, arithmetic depends on a specialized brain network in the parietal lobes (Dehaene et al., 2004; Zago et al., 2001) and on a system dedicated to sets and their cardinal numbers in the anterior intra-parietal sulcus (IPS; Castelli et al., 2006). In this sense, poor arithmetic performance is shown to be associated with abnormalities in the IPS (Molko et al., 2003). Thus, similar to what has been suggested for word reading, right lateralization for number processing in posterior areas could be the result of comparable top-down effects from higher-order areas. Interestingly, Park and colleagues (Park et al., 2012) found that the lateralization of numerical processing in parietal cortex predicted lateralization of visual number form processing in visual cortex and suggested that these results are consistent with the hypothesis of top-down influences from parietal numerical activity in the neural localization of number

recognition in ventral visual cortex. Our data, although clearly demonstrating that numbers are processed through a right lateralized circuit, also show a late effect in the left intraparietal sulcus. Moreover, there appears to be temporal overlap of activation between occipito-temporal (fusiform) regions and other temporal regions (superior and middle). Therefore, a combination of feed-forward and feedback mechanisms may be involved in number processing. Further research is needed to understand this novel finding.

It is important to note that our findings do not completely align with some previous reports of patients with unilateral left hemisphere lesions that resulted in pure alexia: visual word recognition deficit. These patients were severely impaired in reading Arabic numerals aloud, although they maintained the ability to make magnitude judgments, deciding which one of two quantities was larger (Cohen and Dehaene, 1995, 2000; see also Starrfelt and Behrmann, 2011). According to this dissociation between impaired reading and preserved comprehension of Arabic numerals in patients with left hemisphere damage, bilateral number processing would be expected; however, our results show mostly a right lateralized network, except for an effect in the left intra-parietal sulcus and bilateral activation in the fusiform at 150 ms when contrasting the activation of numbers against a previous baseline of null events. (Note that this was not the case when comparing numbers versus any of the other conditions: words, pseudowords, symbols or consonant strings. All these comparisons showed a right lateralized increase of activation for numbers.) Several possibilities can account for this discrepancy. First, our task does not require the verbalization of Arabic numerals, and thus, there is no need to activate the left lateralized network. Second, the activated areas in the right hemisphere of the present study are not strictly necessary for reading words and digits, and only the areas in the

ventral stream that showed activation for all stimuli when compared with the null event (pre-stimulus) baseline are necessary and shared for the processing of all stimulus types. Note that all stimuli showed activation in ventral areas at 150 ms, although to different extents and intensities and also that numbers showed right hemisphere activation. Consequently, differences were evident when direct contrasts between stimuli were performed. While the present data advance our understanding of the brain circuits involved in word and number processing, they cannot adjudicate between these two possibilities and the apparent discrepancy with the patient data. Additional experiments are necessary to better understand the circuit responsible for digit processing and the extent to which it overlaps with the circuits implicated in reading.

In summary, we investigated the underlying spatial and temporal brain dynamics of word and number processing using MEG. A dissociated pattern of processing pathways that originates in the early stages of processing emerged for words and numbers. Word processing follows a left lateralized pathway, while visual number processing follows a more right lateralized pathway. While the reason for these distinct pathways remains unclear, it appears to be related to the lateralization of higher order mechanisms for language processing, and visuo-spatial attention and numerical cognition, respectively. Moreover, the processing of alphanumeric stimuli seems to engage networks with bidirectional temporal dynamics of information flow that involve feedback from temporal and parietal regions (e.g., the angular gyrus for alphabetic stimuli). Future research is required to investigate the neural mechanisms that support the processing of digits as visual symbols in other cultures that use different visual notations, and furthermore, to explore the cause of the reported distinct pathways and the temporal dynamics of number processing.



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## Figure captions

**Figure 1:** Regions Of Interest (ROIs) selected for statistical comparison between each experimental condition (Words, Pseudowords, Consonant strings and Numbers) and the control condition (Symbol strings). Each ROI was selected from the Destrieux et al., (2010) brain parcellation implemented in FreeSurfer. The ROIs in four views of the left hemisphere are overlaid on the averaged brain. The homologous right hemisphere regions were also analyzed.

**Figure 2:** Source activity (dSPM noise-normalized z-scores, compared to the baseline) for each experimental condition (Symbols, Consonants, Numbers, Words, Pseudowords) in the occipital-temporal ventral regions (120–180 ms) with a corresponding example stimulus on the left.

**Figure 3:** Differential activity (dSPM noise-normalized z-scores) between experimental conditions and the control Symbols condition in occipital and inferior occipital-temporal regions bilaterally. Grey bars indicate the time-intervals in which significant effects were observed.

**Figure 4:** Activation for Numbers compared to Symbols. The brain rendering in the center shows the bilateral activity (dSPM noise-normalized z-scores, compared to the pre-stimulus baseline activity) for Numbers (350–450 ms). Individual plots reflect the time-course of the average activity for Numbers (red line) and Symbols (black line) in

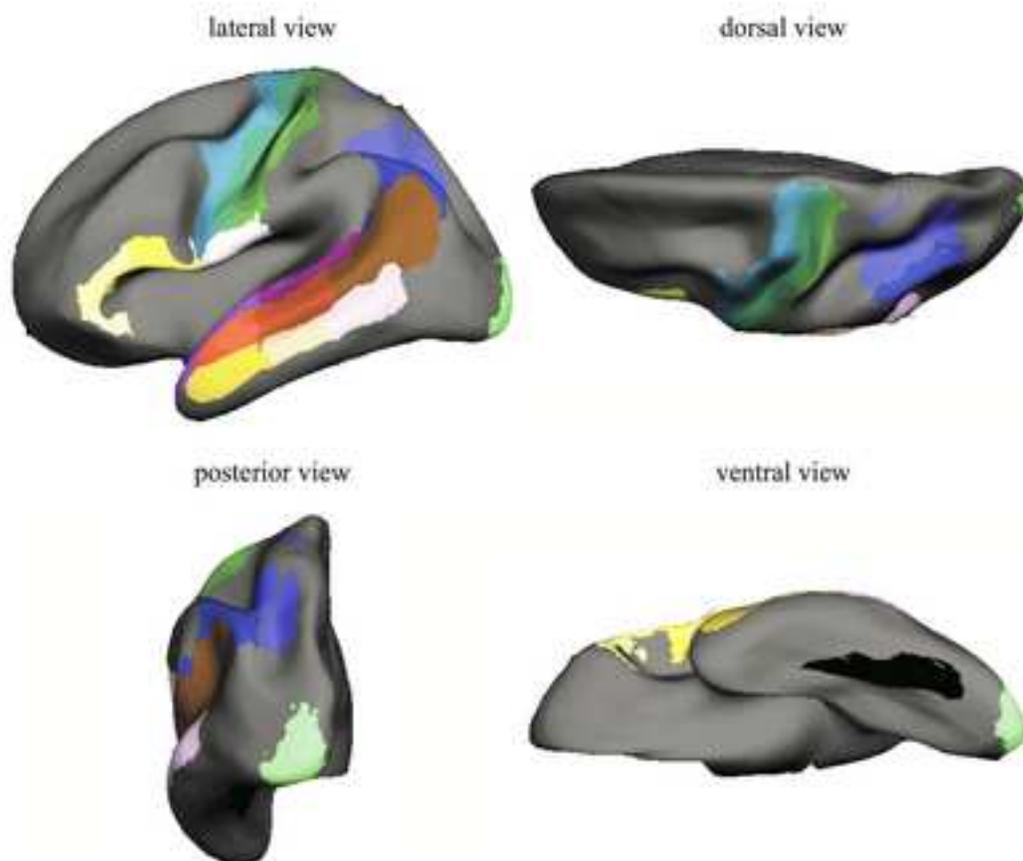
each Region Of Interest in the two hemispheres. Grey bars indicate the time-intervals in which increased activity for Numbers was observed compared to Symbols.

**Figure 5:** Activation for Pseudowords compared to Symbols. The brain rendering in the center shows the bilateral activity (dSPM noise-normalized z-scores, compared to the pre-stimulus baseline activity) for Pseudowords (350–450 ms). Individual plots reflect the time-course of the average activity for Pseudowords (green line) and Symbols (black line) in each Region Of Interest in the two hemispheres. Grey bars indicate the time-intervals in which increased activity for Pseudowords was observed compared to Symbols.

**Figure 6:** Activation for Words compared to Symbols. The brain rendering in the center shows the bilateral activity (dSPM noise-normalized z-scores, compared to the pre-stimulus baseline activity) for Words (350–450 ms). Individual plots reflect the time-course of the average activity for Words (blue line) and Symbols (black line) in each Region Of Interest in the two hemispheres. Grey bars indicate the time-intervals in which increased activity for Words was observed compared to Symbols.

**Figure 7:** Direct statistical contrast between the Words and Numbers conditions, highlighting the left-hemispheric lateralization for the former condition and the right hemispheric lateralization for the latter condition across the Regions of Interest.

9. Figure  
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- |   |   |   |  |
|---|---|---|--|
|  | Inferior Frontal Gyrus<br>(opercularis, triangularis,<br>orbitalis) |  | Occipital Pole   |
|  | Subcentral Gyrus  |  | Fusiform Gyrus   |
|  | Precentral Gyrus, Central<br>Sulcus, Postcentral Gyrus              |  | Superior Temporal Gyrus<br>(Anterior, Posterior)             |
|  | Angular Gyrus   |  | Superior Temporal Sulcus<br>(Anterior, Medial,<br>Posterior) |
|  | Inferior Parietal Sulcus  |  | Medial Temporal Gyrus<br>(Anterior, Medial,<br>Posterior)    |

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### Early activation ~150 ms

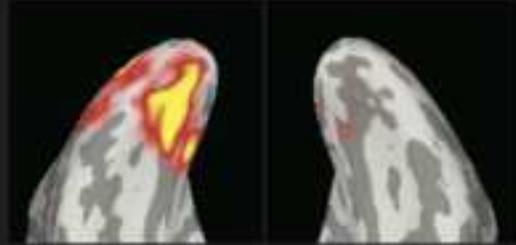
#### Symbols

%+! ?>



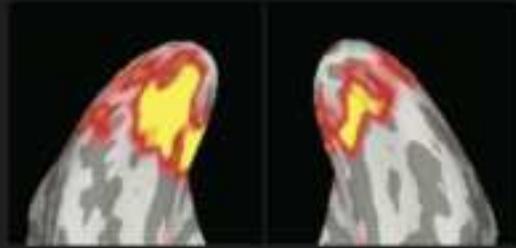
#### Consonants

SRNTL



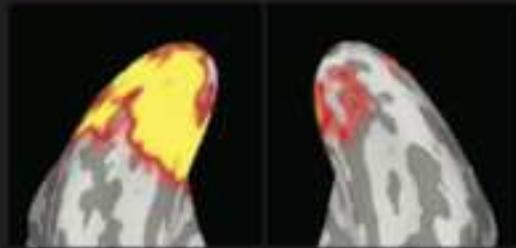
#### Numbers

71593



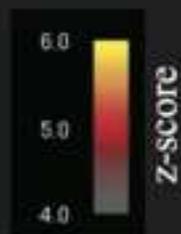
#### Words

TRONO



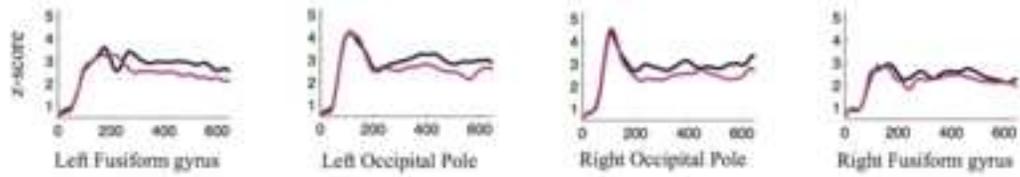
#### Pseudowords

TOCLE

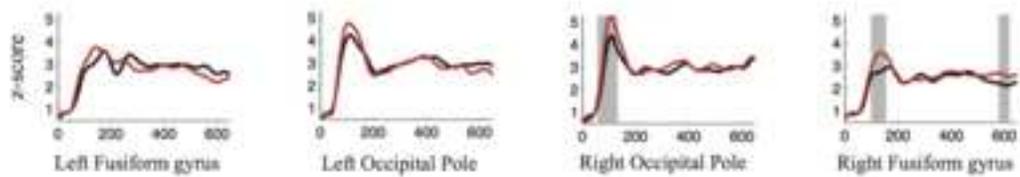


## Differential activation in occipital-temporal regions

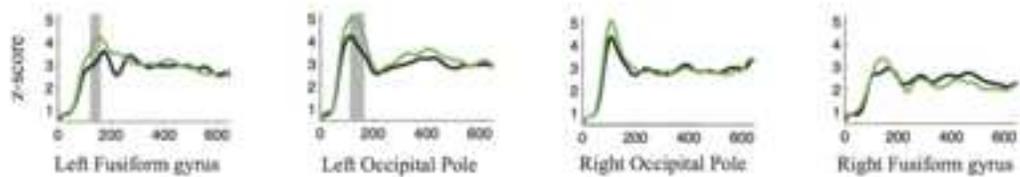
### a. Consonant strings > Symbols



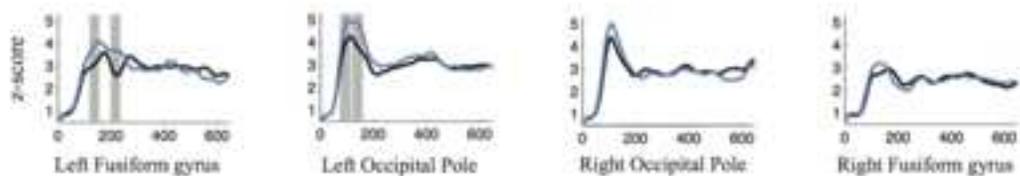
### b. Numbers > Symbols



### c. Pseudowords > Symbols

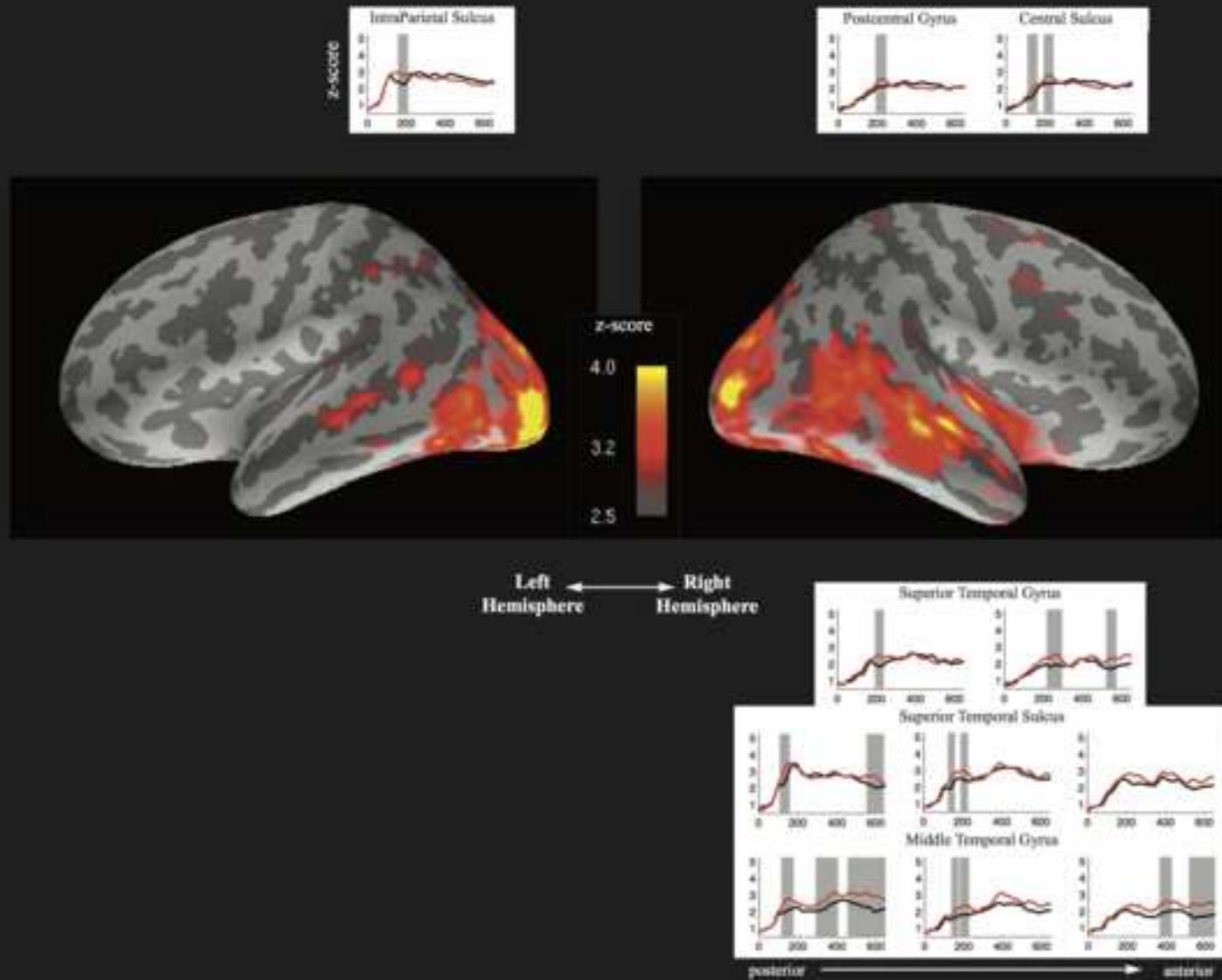


### d. Words > Symbols

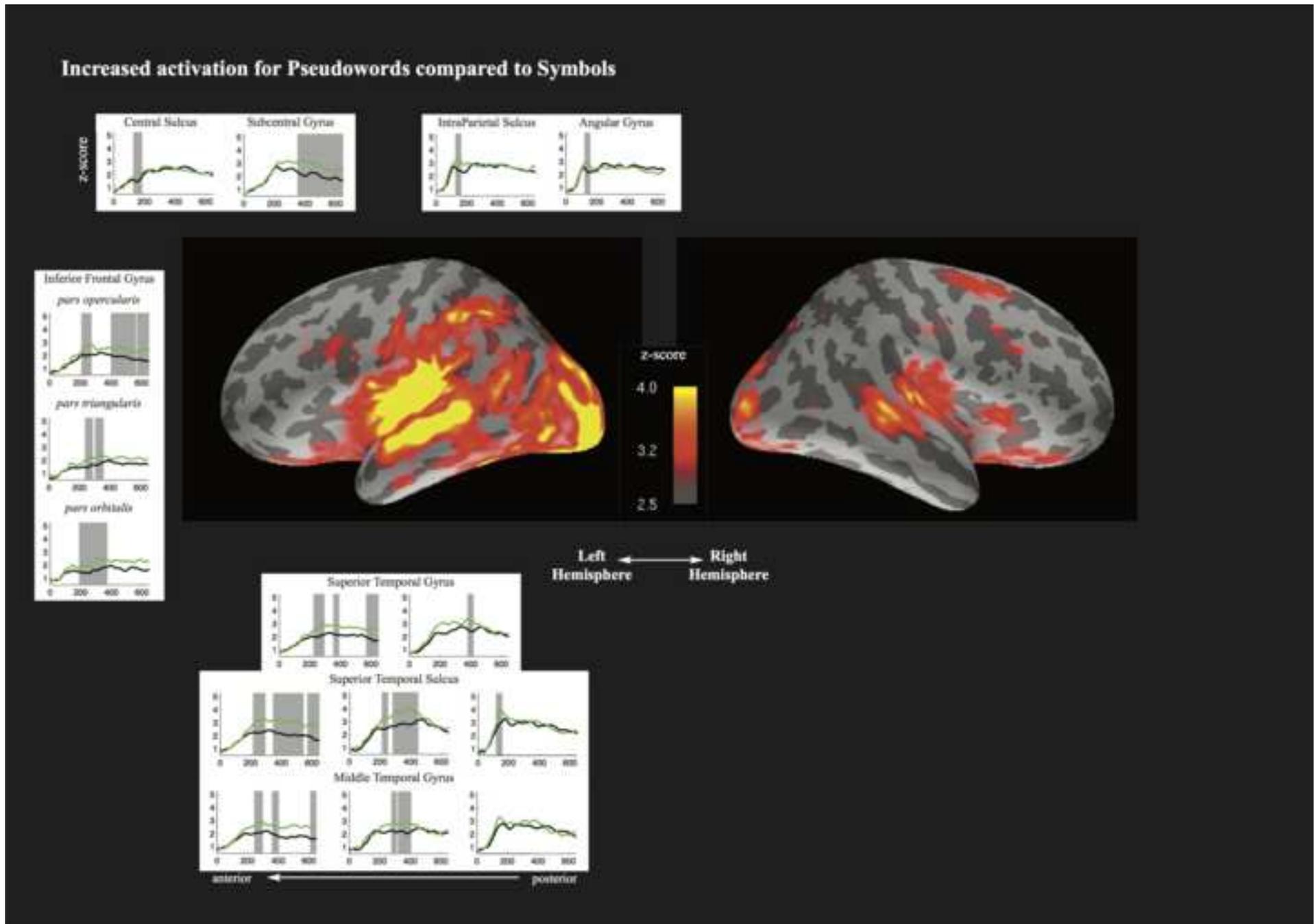


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### Increased activation for Numbers compared to Symbols

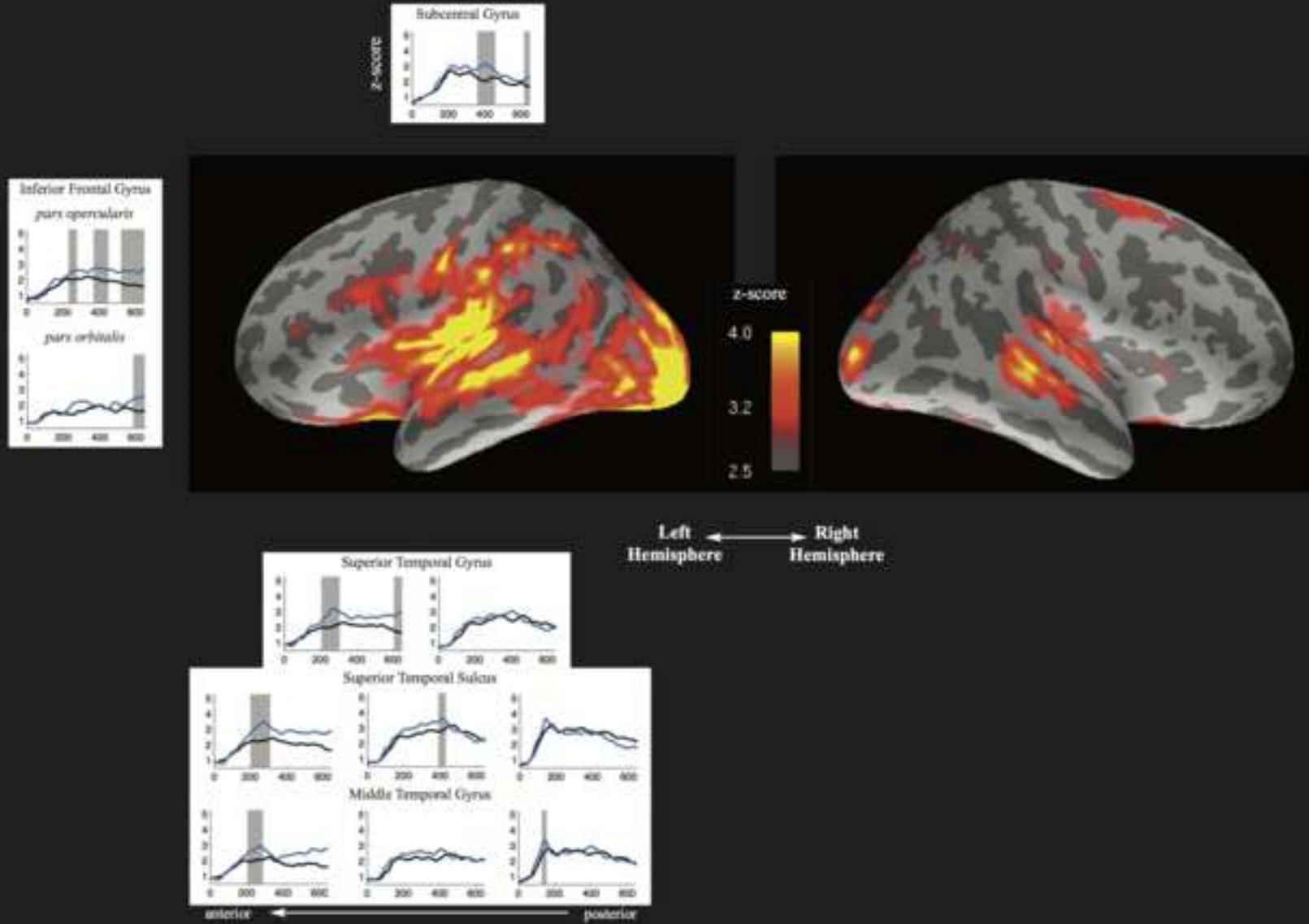


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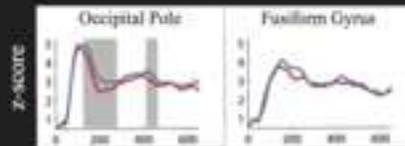
### Increased activation for Words compared to Symbols



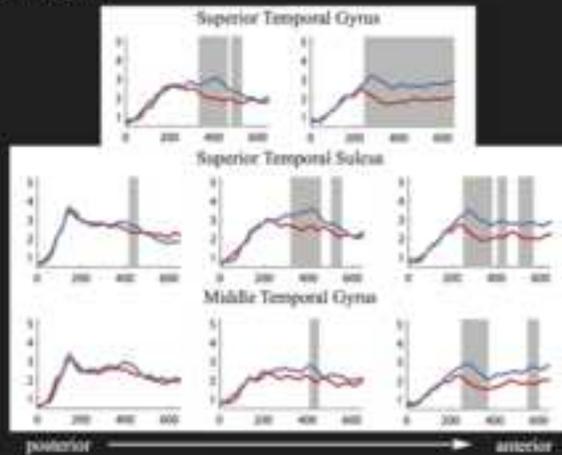
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### Left hemisphere: Words > Numbers

Visual regions



Lateral Temporal regions

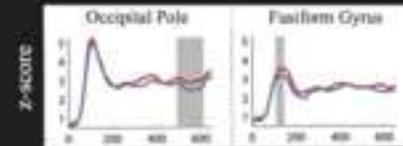


Inferior Frontal regions

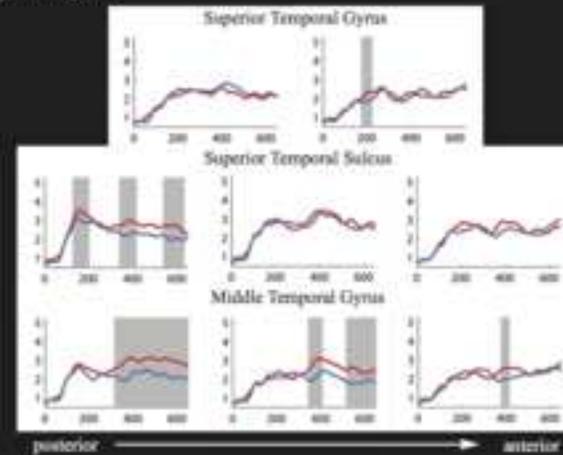


### Right hemisphere: Numbers > Words

Visual regions



Lateral Temporal regions



Inferior Frontal regions

