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Research Report

Brain-wide decoding of numbers and letters: Converging evidence from multivariate fMRI analysis and probabilistic meta-analysis

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ABSTRACT

Previous studies exploring category-sensitive representations of numbers and letters have predominantly focused on individual brain regions. This study expands upon this research through computationally rigorous whole-brain neural decoding using Elastic Net (ND-EN), facilitating the analysis of neural patterns across the entire brain with greater precision. To establish the robustness and generalizability of our results, we also conducted innovative probabilistic meta-analyses of the extant functional neuroimaging literature. The investigation comprised both an active task, requiring participants to distinguish between numbers and letters, and a passive task where they simply viewed these symbols. ND-EN revealed that, during the active task, a distributed network—including the ventral temporal-occipital cortex, intraparietal sulcus, middle frontal gyrus, and insula—actively differentiated between numbers and letters. This distinction was not evident in the passive task, indicating that the task engagement level plays a crucial role in such neural differentiation. Further, regional neural representational similarity analyses within the ventral temporal-occipital cortex revealed similar activation patterns for numbers and letters, indicating a lack of differentiation in regions previously linked to these visual symbols. Thus, our findings indicate that category-sensitive representations of numbers and letters are not confined to isolated regions but involve a broader network of brain areas, and are modulated by task demands. Supporting these empirical findings, probabilistic meta-analyses conducted with NeuroLang and the Neurosynth database reinforced our observations. Together, the convergence of evidence from multivariate neural pattern analysis and meta-analysis advances our understanding of how numbers and letters are represented in the human brain.

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1. Introduction

The ability to decode visual symbols, such as numbers and letters, is a fundamental component of human cognitive skills, playing a critical role in literacy and numeracy (Ansari, 2008; Dehaene & Dehaene-Lambertz, 2016; Menon & Chang, 2021). For the past two decades, research investigating the neural representations of these symbols has primarily focused on the ventral temporal-occipital cortex (VTOC), a region known for its involvement in specialized visual processing (Behrmann & Plaut, 2013; Grill-Spector & Weiner, 2014; Kanwisher, 2010; Nestor, Plaut et al., 2011). Much of this work has concentrated on specific areas within the VTOC, such as the visual word form area, which is thought to be particularly sensitive to letters and words (Cohen & Dehaene, 1995; Dehaene & Dehaene-Lambertz, 2016; Plaut & Behrmann, 2011; Vogel, Petersen et al., 2014). Additionally, researchers have explored the existence of number form areas, hypothesized to be sensitive to processing numerical symbols (Shum, Hermes et al., 2013; Grotheer, Herrmann et al., 2016; Yeo, Pollack et al., 2020; Cai, Hofstetter et al., 2023). Despite these collective efforts, the precise nature of category-sensitive neural representations for numbers and letters — and the extent to which they depend on distributed brain networks beyond the VTOC — remains incompletely understood. Comprehending such complex neural patterns would require computationally intensive decoding of high-dimensional data across a vast number of voxels encompassing the entire brain, which has been a significant challenge until recent advances in machine learning approaches.

For the visual processing of numerical symbols, previous studies have predominantly focused on the VTOC, and the extent to which category-sensitive responses could be more robustly represented in distributed brain areas beyond the VTOC remains underexplored. While intracranial electrophysiological studies involving a small number of patients have proposed the existence of a number form area in the lateral VTOC, suggesting its unique role in number processing (Shum, Hermes et al., 2013; Hermes, Rangarajan et al., 2017), fMRI studies in neurotypical individuals have yielded inconsistent findings on category-sensitive responses in the VTOC (Pollack & Price, 2019; Price & Ansari, 2011; Grotheer, Jeska et al., 2018; Merkley, Conrad et al., 2019). Recent meta-analyses of fMRI studies suggest that distinct neural representation of numbers is not confined to the VTOC but spans multiple regions in frontal, parietal, and occipital lobes (Sokolowski, Fias et al., 2017; Yeo, Wilkey et al., 2017). Moreover, the engagement of the VTOC appears to be task dependent, with heightened responses during active processing (Grotheer, Jeska et al., 2018; Pollack & Price, 2019, Cai, Hofstetter et al., 2023) but not during passive viewing (Price & Ansari, 2011) of numbers.

For the visual processing of letters, there has been extensive investigation of the role of the VTOC, particularly the visual word form area, which is thought to be involved in recognizing letter shapes and letter strings (Longcamp, Anton et al., 2003; Cohen & Dehaene, 2004, Flowers, Jones et al., 2004). However, there is substantial evidence suggesting that the neural representation of letters extends beyond the VTOC, engaging a distributed network across temporal, parietal, and frontal cortices (James & Gauthier, 2006, Liu, Li et al., 2011; Lochy, Jacques et al., 2018; Long, Yang et al., 2020; Vin, Blauch et al., 2024). While current evidence points to a distributed neural representation for letter symbols, the context in which these representations extend beyond the VTOC remains unclear. Additionally, the literature has been limited in terms of whole-brain analysis, raising questions about whether letter symbols are robustly represented across the entire brain in a manner similar to, or different from, number symbols. Critically, it is unknown whether these potential similarities or differences in neural representations persist under comparable task contexts, as few studies have directly compared number and letter processing using identical paradigms across the whole brain.

Collectively, these findings indicate that the sensitivity of individual areas within the VTOC to number or letter symbols remains ambiguous and may be influenced by task demands or context. This suggests that the VTOC may not be as specialized for neural representation of categories of visual symbols as previously thought. Critically, the extent to which category-sensitive responses to numbers or letters are more robustly encoded in distributed brain areas is poorly understood. This gap in knowledge underscores the need for a broader exploration of how the brain processes these fundamental symbols in a network of regions that extends beyond individual brain areas such as the VTOC.

Here we apply quantitatively rigorous procedures to probe whole-brain decoding of neural representations for numbers and letters under different task contexts. Our aim is to provide a more comprehensive understanding of how these symbols are represented in the human brain, addressing the limitations of previous research that has focused primarily on specific brain regions. Specifically, we utilized multivariate neural pattern analysis techniques that have emerged as powerful tools for investigating the intricate structure of neural representations and how the brain organizes and discriminates between category-sensitive information (Haxby, Connolly et al., 2014, Diedrichsen & Kriegeskorte, 2017; Hebart & Baker, 2018, Kragel, Koban et al., 2018).

We employed two distinct multivariate pattern analysis approaches to investigate the neural representation of numbers and letters. The first approach employed a whole-brain neural decoding with Elastic Net (ND-EN) (Zou & Hastie, 2005, Cho, Ryali et al., 2011; Bulthé, De Smedt et al., 2014). ND-EN is particularly well-suited for examining intricate neural representations across the brain, a key aspect of our study. This method offers several key advantages in this context. First, ND-EN can handle the complexities of high-dimensional brain imaging data, striking a balance between model complexity and prediction accuracy. This is achieved by combining the strengths of both ridge and lasso regression techniques, through L1 and L2 regularization, within the Elastic Net framework (Zou & Hastie, 2005). Second, ND-EN can identify task-relevant patterns and connections, enabling the integration of information from distributed brain regions, overcoming limitations of univariate and other multivariate methods. We supplemented this analysis with neural representational similarity (NRS) analysis (Xue, Dong et al., 2010; Qin, Cho et al., 2014; Schlichting, Mumford et al., 2015). This analysis enabled us to examine whether individual regions, such as the VTOC, encode numbers and letters similarly, providing a more detailed view of category-specific neural representation within these key areas.

In the empirical research component of our study, we first applied ND-EN to investigate how distributed brain areas collectively contribute to the differentiation between representations of numbers and letters. Subsequently, we utilized neural representational similarity (NRS) analysis to examine whether numbers and letters elicit similar activation patterns in specific brain areas of interest. Our hypothesis was that a distributed network, including subdivisions of the VTOC and posterior parietal cortex, would jointly represent various categories of visual symbols. Given existing evidence that category-specific neural representations are modulated by attention (Pollack & Price, 2019; Price & Ansari, 2011; Grotheer, Ambrus et al., 2016; Grotheer, Jeska et al., 2018; Merkley, Conrad et al., 2019), we examined whether the similarity or differentiation between numbers and letters would vary between active and passive task contexts (Fig. 1A–C). We predicted that in conditions where attention is actively directed towards numbers or letters, the differentiation between these categories would be more pronounced in the distributed network.

To test our hypothesis, we employed two distinct fMRI datasets, each corresponding to two distinct task states. The first dataset, acquired at Stanford, involved an active task, where participants were presented with sequences of numbers and letters and required to determine whether an item had been shown previously. This task was designed to actively engage participants' attention and working memory. The second dataset, sourced from an open-access study (Merkley, Conrad et al., 2019), involved a passive task where participants simply viewed numbers and letters, occasionally responding to color changes in a fixation point. This passive task allowed us to examine neural responses to symbolic stimuli under minimal attentional demands.

In previous analysis of the passive task dataset (Merkley, Conrad et al., 2019) the authors conducted univariate analyses comparing number and letter conditions with various control stimuli. A related study employed multivariate pattern analysis to examine the neural representation of numbers and letters specifically within subregions of the VTOC (Yeo, Pollack et al., 2020). However, in both approaches, findings regarding differentiation of numbers and letters in the VTOC were inconclusive due to limited scope of regional analysis. Our study significantly extends these analyses to explore whole-brain patterns of neural activity, allowing us to assess category-sensitive representations for numbers and letters across a broader neural network and across different task states. This novel approach enables a more comprehensive understanding of how task context modulates distributed neural coding of visual symbols.

In the meta-analysis component of our study, we sought to extend and generalize our findings using a large-scale neuroimaging data from 14,371 fMRI studies in the Neurosynth database (Yarkoni, Poldrack et al., 2011). To achieve this, we employed NeuroLang (https://neurolang.github.io; Iovene & Wassermann, 2020), an advanced probabilistic logic language specifically designed to quantify the degree of association between regional brain activation and cognitive terms of interest. This innovative approach allowed us to integrate findings from a broad array of literature, thereby facilitating a comprehensive evaluation of our hypotheses concerning category sensitivity for numbers and letters in distributed brain regions.

We conducted a series of forward meta-analyses to identify brain regions uniquely associated with numbers or letters. Our hypothesis was that processing of these categories would involve distinct, distributed brain regions. Subsequently, we conducted a series of reverse meta-analyses (CogAt; Poldrack, Kittur et al., 2011); to determine cognitive functions most frequently associated with specific VTOC subdivisions. We tested the hypothesis that these individual subdivisions would show no preference for numbers compared to letters, or vice versa. This comprehensive meta-analytic approach aimed to provide a broader, data-driven perspective on the neural representation of numbers and letters, contextualizing our empirical findings in the wider body of neuroimaging research.

Together, the integration of experimental data and advanced multivariate and meta-analytic techniques in our study offers a more comprehensive understanding of how the brain encodes numbers and letters. These findings contribute significantly to our knowledge of distributed coding of visual symbols in the brain, illuminating the broader principles underlying perception and cognition.

2. Materials and methods

2.1. *Participants*

We used two fMRI task datasets from two independent cohorts of participants. The first cohort comprised 49 adolescents and young adults who completed an active number-letter task (14–21 years; mean age = 18.4 ± 1.5 years; 24 females). These data were acquired at Stanford University. Data from 12 participants were excluded due to excessive head motion during MRI scans or incomplete fMRI task data. The final sample included 37 participants (14–21 years; mean age = 18.5 ± 1.5 years; 21 females). The second cohort comprised 43 adults who completed a passive task (18–39 years; mean age = 25.3 ± 5.8 years; 28 females) (Merkley, Conrad et al., 2019). These data were obtained from OpenNeuro (https://openneuro.org/datasets/ds002033/versions/1.0.0) open-source dataset. Data from 3 participants were excluded due to left handedness and 3 participants were removed due to incomplete fMRI task data. The final sample included 37 participants (18–39 years; mean age = 25.1 ± 5.9 years, 26 females).

All participants included in the current study were right-handed. No participants reported neurological, psychiatric, or vision disorders. All adult participants provided written informed consent. For participants under 18 years old, we obtained written informed consents from their parents/legal guardians and assent from participants. All participants received monetary compensation for their participation. The

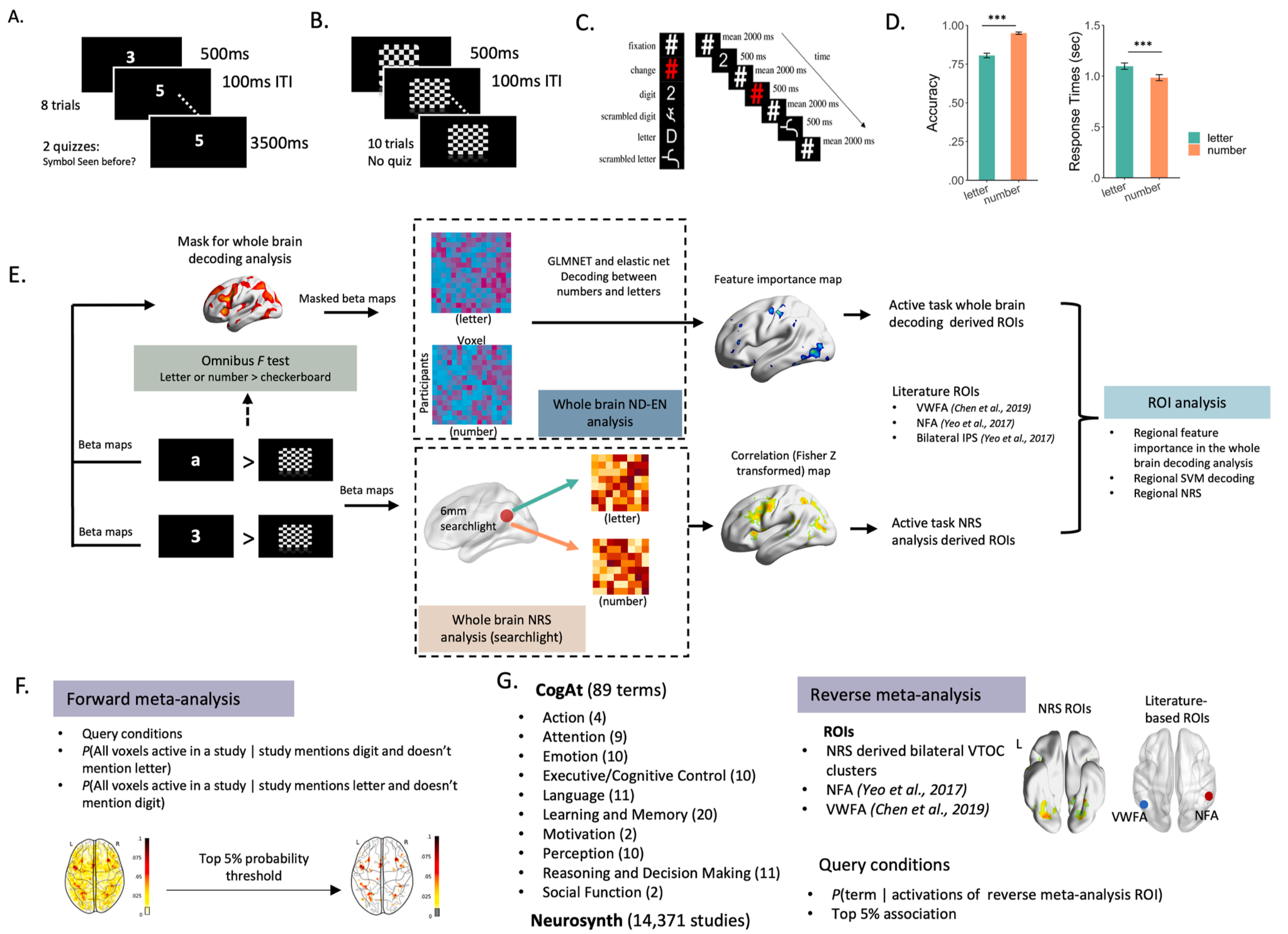

Fig. 1 – Active and passive fMRI tasks were used to investigate regional and distributed brain representations of numbers and letters. (A–B) Active fMRI task: Experimental condition. Numbers or letters were shown in separate blocks, in which participants attended to a series of 8 numbers or letters (see also *Methods* for details). During two subsequent probe trials participants indicated whether they had seen the presented number or letter in the same block . (B) *Active fMRI task*: *Control condition*. A checkerboard block, which had the same total number of trials (10 trials) as the experimental condition without administration of probe trials, was used as the control condition. (C) *Passive fMRI task*. Participants completed a change detection task in which they indicated when the color of a hashtag (#) changed from white to red, in a series of trials where visual numbers, letters, non-alphanumeric symbols, and hashtags were presented. Adapted from (Merkley, Conrad et al., 2019). (D) *Behavioral performance in the active fMRI task*. Participants were significantly more accurate and faster in the number compared to the letter condition. (E) *Analysis pipeline*. Preprocessed fMRI data from the active task were entered into a subject-level General Linear Model (GLM) to obtain activation maps for number > checkerboard contrast and letter > checkerboard contrast. These two maps were used in whole-brain neural decoding with Elastic Net (ND-EN) and neural representational similarity (NRS) analysis. An Elastic Net classifier was used in whole-brain ND-EN analysis. The Elastic Net penalizes voxels with low weights and produces a weight (feature importance) map. The NRS analysis used a whole-brain searchlight algorithm with 6-mm search radius. The passive task followed analogous analysis pipeline with relevant task contrasts (see *Methods* for details). Literature-based regions of interest (ROIs) were used for ROI-based analyses for active and passive fMRI tasks. (F–G) A series of forward and reverse meta-analyses were performed based on the Neurosynth database. Terms and brain regions identified at top 5% probability were considered significant results from meta-analyses. (F) *Forward meta-analysis*. The probability of all voxels mentioned in a study where the first term was mentioned but the second term was not mentioned was assessed. "digit" and "letter" terms were used as first and second terms (or vice versa). (G) *Reverse meta-analysis*. The probability of each of 89 cognitive atlas terms associated with the activation of a given ROI across extant fMRI literature was assessed. The bilateral VTOC derived from the NRS analysis and literature-based number form area (NFA) and visual word form area (VWFA) were used as ROIs. $^{***}p < .001$.

study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institution.

2.2. *Experimental design and statistical analysis*

We examined distinct and shared neural representation of visual numbers and letters in two sets of visual number and letter processing fMRI tasks that differed in task demand: active (high task demand) and passive (low task demand) tasks. For behavioral data analysis, two-tailed paired *t*-tests were conducted to compare participants' response time and accuracy between number and letter conditions in the active task. For the passive task, behavioral data were not provided in the open-source dataset and were not analyzed. Details of fMRI task design and statistical analyses of fMRI data are described below.

2.2.1. *fMRI task design*

Active task. Participants completed a symbolic delayed match-to-sample task in the MRI scanner, which consisted of two runs of number condition and two runs of letter condition (Fig. 1A). The task was programmed in Psychopy (Peirce, Gray et al., 2019) with a short block design. In each run, which lasted 5.5 min, 8 blocks of symbol condition (letter or number) and 8 blocks of visual baseline condition (black and white checkerboard) were presented. These 16 blocks were presented in a pseudo-randomized order with no more than 2 blocks from the same condition being presented consecutively. Each block started with a 10-s-long fixation, followed by 10 trials. In each trial (except for the last two probe trials for the symbol block; see below), a stimulus (an Arabic numeral, an alphabet in lower case, or a black and white checkerboard) was presented for 500 msec, followed by a 100 msec interstimulus interval. At the end of each symbol block, two 3.5 sec probe trials were presented. During the probe phase, participants were asked to press a key to indicate whether or not they saw the presented symbol in the current block. Each symbol block lasted 23 sec and each checkerboard block lasted 16 sec.

All stimuli were presented using an LCD projector and a back-projection screen in the scanner. The Arabic numerals were selected from 0 to 9 and the alphabetical letters were selected from “a” to “z”. Since the probability of a number being shown in each trial is higher than the probability of a letter being shown, the frequency of each number/letter being presented was counterbalanced across symbol blocks. A 72×72 pixel-checkerboard image was used in checkerboard blocks. The height of the symbols and fixation was set at 50 pixels. The symbols were presented with a white color font at the center of a 1024×768 black screen.

Passive task. A detailed description of the passive task can be found in a previous publication (Merkley, Conrad et al., 2019). Briefly, participants passively viewed various types of symbols in the scanner (Fig. 1B). They were instructed to pay attention to the color change of the fixation (a white hashtag) and press a key when the color changed to red. Arabic numerals from 1 to 9 and 9 capitalized letters L, S, N, R, P, E, D, C and G were used for generating the standard symbol, mirrored symbol, and scrambled symbol conditions. The scrambled symbols were generated by manually segmenting and rearranging the standard symbol into a novel shape. Each stimulus was presented twice in a run, which included a total of 108 trials. In addition, 6 catch trials with the red hashtag as the stimulus were included for participants to detect the color change. Each trial started with a fixation (a white pound sign) that lasted either 1000, 2000, or 3000 msec. The stimulus was presented for 500 msec. Participants completed a total of 4 runs of the passive task in the scanner. Each run started with a fixation for 16 sec and ended with a fixation for another 16 sec for a stabilized baseline. Compared to the active task, the passive task was less likely to require cognitive resources to maintain the symbols in working memory throughout each run.

2.2.2. *MRI data acquisition and preprocessing*

Active task. Task-based functional MRI data were acquired on a 3T GE scanner using a T2* weighted gradient echo-spiral in–out pulse sequence (TR = 2000 msec, TE = 30 msec, FOV = 220 mm^2, matrix size = 64×64, pixel size = 3.4375 mm, slice thickness = 4 mm, flip angle = 80°). A T1-weighted, high-resolution structural image was acquired for the anatomical co-registration of functional images (slice thickness 1 mm; in-plane resolution: 256×256, voxel size = $1.5 \times .9 \times 1.1$ mm^3). All functional images were preprocessed using SPM12 (Ashburner, Barnes et al., 2020). The first five volumes of each time-series were discarded to allow for signal equilibration. The preprocessing pipeline included realignment, slice-timing correction, co-registration to subjects' structural T1 images and normalization to a 2 mm MNI152 template, and smoothing using a 6 mm full-width half-maximum Gaussian kernel to decrease spatial noise. Volumes with greater than .5 voxel scan-to-scan displacement along linear or rotational axes were de-weighted, as well as volumes with greater than 5% change in global signal. The proportion of volumes with scan-to-scan displacement higher than .5 voxel did not exceed 10% across tasks. To account for potential influences of unmatched head motion between groups, head motion parameters were included as covariates of no interest in fMRI general linear model analysis.

Passive task. Details of the high-resolution T1 and T2*-weighted sequences can be found in the previous publication (Merkley, Conrad et al., 2019). In short, the images were acquired at a 3T Siemens Prisma Fit MR scanner using a 32-channel head coil (Siemens, Erlangen, Germany). An MPRAGE sequence was used (TR = 2300 msec; TE = 2.98 msec; flip angle = 9°; in-plane resolution = 256×256 pixels; voxel size = $1 \times 1 \times 1$ mm) for the T1 image and a single-shot gradient-echo planar sequence (TR = 1000 msec, TE = 30 msec, FOV = 208×208 mm, flip angle = 40°, voxel size = $2.5 \times 2.5 \times 2.5$ mm) was used for the functional image. For the analysis included in the current study, we used the same preprocessing procedures as the active task dataset described above for the passive task dataset and confirmed that original GLM results remained consistent across preprocessing procedures.

2.2.3. *Functional MRI data analysis*

2.2.3.1. INDIVIDUAL LEVEL GENERAL LINEAR MODEL (GLM). ***Active task.*** Individual level fMRI data was fit with a general linear model (GLM) using SPM12 (Ashburner, Barnes et al., 2020). Separate models were used for the number and letter tasks. For each task, four task-relevant regressors (number/letter, checkerboard, probe, and fixation) were modeled with a box-car function convolved with a canonical hemodynamic response function (HRF). In addition, 6 motion regressors entered the GLM to control for head motion during the task. First-order autoregressive model was used to address the autocorrelation in the fMRI time series. For each task, three contrasts of interest were generated (number/letter − fixation, checkerboard − fixation, and probe − fixation). The number/letter − fixation and the checkerboard − fixation contrasted was used to generate the number > checkerboard and letter > checkerboard contrasts, which was used in further analyses.

Passive task. We used a same box car function convolved with an HRF to model the 6 task regressor (number, letter, mirrored number, mirrored letter, scrambled number, scrambled letter). First-order autoregressive model and the 6 motion regressors were used to capture the autocorrelation in the signal and the head motion. Following the analysis in the original published paper based on this dataset, we adopted the number − scrambled number and letter − scrambled letter as the base contrast for further analyses.

2.2.3.2. Neural decoding with Elastic Net (ND-EN) analysis. In order to examine the hypothesis that distributed regions in the brain jointly contributes to the differentiation between visual numbers and letters, we implemented a multivariate whole-brain ND-EN analysis. Specifically, to classify numbers versus letters, we fit a generalized linear model with Elastic Net regularization using Python package glmnet_python (Balakumar, Hastie et al., 2016) and a leave-one-subject-out cross-validation procedure.

Glmnet solves the problem

$$\min_{\beta_0,\beta}\frac{1}{N}\sum_{i=1}^{N}\omega_i l(y_i,\beta_0+\beta^T x_i)+\lambda\left[\frac{(1-\alpha)||\beta||_2^2}{2}+\alpha||\beta||_1\right]$$

over a grid of values of λ, which controls the overall strength of the penalty, covering the entire range of possible solutions (Friedman, Hastie et al., 2010). Here, N is the number of observations; i indicates the i-th observation; ω_i is a weight applied to each observation (default is 1); β are the coefficients of the model; x_i are the features of observation i; y_i is the class label of observation i; $l(y_i,\beta_0+\beta^T x_i)$ is the negative log-likelihood contribution for observation i. The Elastic Net penalty is controlled by α, the mixing parameter that determined the balance between Lasso (L1) and Ridge (L2) penalties. When $\alpha = 1$, the penalty $||\beta||_1$ is purely Lasso (L1 norm). When $\alpha = 0$, the penalty $||\beta||_2^2$ is purely Ridge (L2 norm). Intermediate values of α give a mixture of Lasso and Ridge, which is Elastic Net penalty. Here, we assigned .1 to α for a moderate level of penalty.

The Ridge penalty shrinks the coefficients of correlated features towards each other but cannot perform variable selection, meaning it keeps all features in the model with reduced magnitudes (Hoerl & Kennard, 1970). In contrast, Lasso tends to select a small number of important features by shrinking some coefficients to zero, effectively discarding the less important ones, but it struggles when features are highly correlated, often selecting one feature from a group and discarding others (Tibshirani, 1996). Elastic Net combined the strengths of both methods, incorporating Lasso's feature selection ability and Ridge's handling of correlated features (Zou & Hastie, 2005). This makes it an optimal approach for a whole brain decoding analysis, where there is a large number of correlated features.

In our analysis, all voxels within an omnibus-F-test-based mask, which was generated by detecting voxels showing stronger activation in numbers or letters compared to checkerboard and thresholding at voxel-wise FDR corrected $p < .01$, were fed into Elastic Net as features. The Elastic Net was trained to classify number and letter using the number > checkerboard and letter > checkerboard contrasts in the active task, and using the number > scrambled and letter > scrambled letter contrasts in the passive task. Permutation tests with 5000 iterations were used to determine the significance of the decoding accuracy. As the Elastic Net estimates the coefficient for each feature to indicate their relevant importance in the decoding, we used the absolute value of these coefficients as a measure of feature importance. We then obtained the peak coordinates from these clusters and generated 6-mm spherical ROIs around the peaks. The mean feature importance value was calculated for each ROI. We additionally examined the significance of the feature importance from literature-based ROIs. To do this, we obtained the mean feature importance from each ROI and compared with the null distribution established on other 5000 mean feature importance values generated in the 5000-iteration permutation.

2.2.3.3. Neural representational similarity (NRS) analysis. Multivariate NRS analysis was implemented to examine which brain regions show similar neural representational patterns between numbers and letters (Kriegeskorte, Mur et al., 2008; Kragel, Koban et al., 2018; Chang, Rosenberg–Lee et al., 2019; Schwartz, Zhang et al., 2021). In this analysis, in each participant, voxel-wise beta values from contrasts of interest were used to calculate spatial correlation between the contrasts to determine the NRS within a 6-mm spherical region. The estimated correlation coefficients were Fisher Z-transformed to generate the NRS for each voxel. In the current study, we examined the NRS between the number > checkerboard and the letter > checkerboard contrast in the active task and number > scrambled number and letter > scrambled letter contrasts in the passive task. We first examined NRS in ROIs based on prior literature, including the NFA and IPS (Yeo, Wilkey et al., 2017) and the VWFA (Chen, Wassermann et al., 2019) (Fig. 3A). Next, a whole brain searchlight algorithm was used to repeat this procedure for all voxels across the whole brain. The individual NRS maps were then entered into one-sample t-tests to compare the mean with zero and generate the group level t-maps, which were thresholded at voxelwise FDR corrected $p < .001$ and extended cluster size threshold of 100 voxels. Based on the peak coordinates in the thresholded NRS map, we generated 6-mm spherical regions of interest (ROIs) around these peak voxels and obtained the mean NRS value from these ROIs.

For NRS in each ROI, *Bayes Factor* (*BF*) was obtained to further assess evidence for H_1 or H_o (Keysers, Gazzola et al., 2020), using the *BayesFactor* package (Morey, Rouder et al., 2015) in R 4.1.2 (R Core Team, 2013). *BF* values greater than 3 provide evidence for H_1. *BF* values between .33 and 3 provide absence of evidence. *BF* values below .33 provide evidence for H_o.

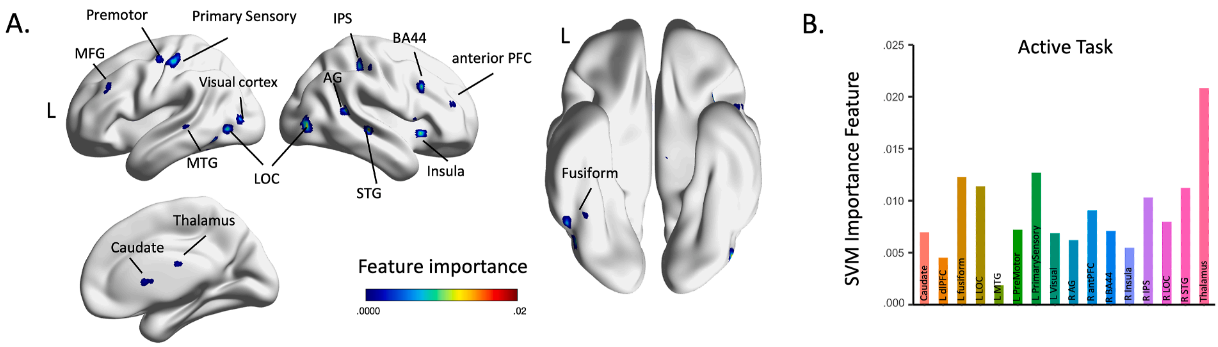

Fig. 2 – Whole-brain neural decoding with Elastic Net (ND-EN) reveals distributed brain areas that jointly differentiate between numbers and letters in the active fMRI task. (A) *Brain regions with non-zero feature importance identified by Elastic Net.* Multiple brain regions had non-zero feature importance, including the bilateral lateral occipital cortex (LOC), left fusiform gyrus, right intraparietal sulcus (IPS), right angular gyrus (AG), right insula, bilateral middle frontal gyrus (MFG), left primary sensory cortex, left premotor cortex, caudate, and thalamus. (B) *Relative feature importance of individual brain regions.* Feature importance that survived the Elastic Net penalty were observed in the thalamus, left primary sensory cortex, left fusiform gyrus, right superior temporal gyrus (STG), right IPS, bilateral LOC, and anterior prefrontal cortex. See also Table 3. L = left; R = right.

2.2.3.4. Regions of interest (ROIs) selection. To examine similarity between neural representations of numbers and letters in the ventral visual stream as well as other brain regions implicated in number processing [e.g., the intraparietal sulcus (IPS)], we used ROIs based on prior literature, including number form area (NFA) and IPS (Yeo, Wilkey et al., 2017), and the visual word form area (VWFA) (Chen, Wassermann et al., 2019) (Fig. 3A) in the active and passive tasks. We used 6-mm spherical ROIs around peak coordinates of the regions reported in previous studies. The peak coordinate of the NFA ROI, which was reported in TAL space in Yeo et al., was converted to MNI space using the MNI Talaraich Tool (BioImage Suite: https://bioimagesuiteweb.github.io/bisweb-manual/tools/mni2tal.html).

2.2.3.5. Meta-analyses of brain regions associated with number and letter processing and cognitive functions associated with the VTOC regions. In addition to the analyses of the empirical data, we performed a series of forward and reverse meta-analyses. In the forward meta-analyses, which identified brain regions associated with a given term, we included published fMRI studies in Neurosynth database using two search terms, *digit* (116 studies) and *letter* (173 studies), available in the database. The term *digit* was used as an alternate term to represent *number*, as the latter term was not available in the database. Here, we used two analytical approaches. First, we estimated the probability of a voxel that appeared in a study where *digit* appeared but *letter* did not. Second, we estimated the probability of a voxel that appeared in a study where *letter* was mentioned but *digit* was not. These analyses yielded two probabilistic brain maps showing clusters associated with studies on *digit* (but not *letter*) or *letter* (but not *digit*). We used the top 5% probability to threshold the resulted probability map.

Next, to determine whether the VTOC is engaged in processing numbers and letters and/or other cognitive functions, we conducted a series of reverse meta-analyses, which identified terms most likely associated with activation of a given ROI. Here we leveraged the Neurosynth (Yarkoni, Poldrack et al., 2011) database consisting of 14,371 published fMRI studies and 89 cognitive atlas terms (CogAt; Poldrack, Kittur et al., 2011). We estimated the log odds ratio of the probability of a search term appearing in a study where activation of an ROI also appears against the probability of the term not

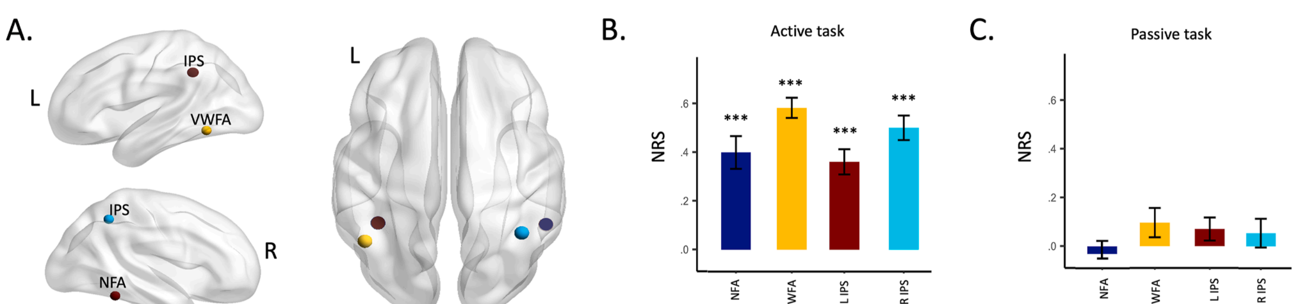

Fig. 3 – Neural representational similarity (NRS) between numbers and letters in the number form area (NFA), visual word form area (VWFA), and intraparietal sulcus (IPS) in active and passive fMRI tasks.
(A) *Regions of interest (ROIs)*. View of selected ROIs from Chen et al. (2019) (VWFA) and Yeo et al. (2017) (NFA and IPS). (B–C) *NRS in literature-based ROIs*. (B) *NRS in the active fMRI task*. High levels of NRS were detected in the NFA, VWFA, and bilateral IPS in the active fMRI task. (C) *NRS in the passive fMRI task*. NRS was low in all ROIs in the passive fMRI task. See also Tables 2 and 3 L = left; R = right; $^{***}p < .001$.

Table 1 – Neural decoding with Elastic Net (ND-EN): Brain areas with different features between numbers and letters in the active fMRI task.

ROI	Feature importance	x	y	z
Left fusiform gyrus	.012	−47	−48	−12
Left lateral occipital cortex	.011	−38	−73	2
Left middle temporal gyrus	.002	−50	−33	−1
Left dorsolateral prefrontal cortex	.005	−36	30	26
Left premotor cortex	.007	−49	−11	53
Left primary sensory cortex	.013	−52	−23	52
Left visual cortex	.007	−28	−80	−1
Right angular gyrus	.006	50	−45	12
Right BA44	.007	47	19	31
Right insula	.005	41	18	−6
Right intraparietal sulcus	.010	27	−46	45
Right lateral occipital cortex	.008	44	−79	2
Right superior temporal gyrus	.011	52	−26	2
Right middle frontal gyrus	.009	44	46	20
Caudate	.007	−6	7	7
Thalamus	.021	8	−15	16

being mentioned where activation of the ROI is mentioned. We performed the reverse meta-analysis on two sets of ROIs, the bilateral VTOC clusters that showed significant NRS in the active task (Fig. 4A) and the VWFA (Chen, Wassermann et al., 2019) and NFA (Yeo, Wilkey et al., 2017) ROIs from the literature (Fig. 3A). The top 5% probability was used as the cut-off threshold. Both forward and reverse meta-analyses were conducted using NeuroLang, a probabilistic logic language (https://neurolang.github.io; Iovene & Wassermann, 2020).

3. Results

3.1. *Behavioral performance in number and letter conditions in the active task*

In the active task, participants were sequentially presented with 8 symbols (numbers or letters) in each symbol block (Fig. 1A). At the end of each symbol block, they were asked to determine whether a number or letter symbol was presented in the current block or not. Participants' accuracy was significantly higher in the number ($M = 94.93\%$; $SD = 4.38\%$) compared to the letter ($M = 81.08\%$; $SD = 8.78\%$) blocks [$t(36) = -9.17$, $p < .001$, Cohen's $d = -2.00$; Fig. 1D]. Response times were significantly faster in the number ($M = 985$ msec; $SD = 180$ msec) compared to the letter ($M = 1098$ msec; $SD = 190$ msec) blocks [$t(36) = 5.69$, $p < .001$, Cohen's $d = .61$; Fig. 1D].

3.2. *Behavioral performance in number and letter conditions in the passive task*

In the passive task, participants were asked to respond to the color change of a fixation symbol (hashtag) (Fig. 1C). It was reported in the original paper that "accuracy on the change detection task was high for all remaining participants ($M = 99.12\%$; $SD = 2.2\%$)" (Merkley, Conrad et al., 2019). Individual participants' behavioral performance data were not provided in the open-source dataset and no further analysis was performed regarding passive task performance.

3.3. *Neural decoding with Elastic-Net (ND-EN) of numbers and letters in the active task*

Our first goal was to determine whether distributed brain areas jointly contribute to differentiation between neural representations of numbers and letters. We used a whole-brain ND-EN approach with an Elastic Net classifier and cross-validation to identify brain areas that jointly contribute to differentiation between numbers and letters. This multivariate ND-EN approach assigned a feature importance value (absolute feature weight) to each voxel across the whole brain (within the mask derived from an omnibus F-test; see **Methods**) to indicate its relative importance in the classification of numbers versus letters. The Elastic Net combined feature elimination from Lasso and feature coefficient reduction from Ridge, and as a result, features with low importance were assigned zero weights.

Table 2 – Neural representational similarity (NRS) between numbers and letters in the active fMRI task.

ROI	*Mean*	*SD*	t	*p*	x	y	z	*Bayes Factor*
Literature-based ROIs								
Number form area (NFA) (Yeo, et al., 2017)	.361	.32	6.97	<.001	52	−47	−18	$3.87*10^{5}$
Visual word form area (VWFA) (Chen et al., 2019)	.581	.25	14.06	<.001	−45	−57	−12	$1.76*10^{13}$
Left intraparietal sulcus (IPS) Yeo et al. (2017)	.400	.41	5.49	<.001	−38	−46	38	$2.03*10^{4}$
Right IPS (Yeo et al., 2017)	.500	.31	9.92	<.001	39	−52	48	$1.17*10^{9}$
Whole-brain NRS-based ROIs								
Left dorsolateral prefrontal cortex	.588	.27	13.18	<.001	−48	24	28	$2.64*10^{12}$
Left parietal cortex (IPS)	.560	.24	13.92	<.001	−32	−54	48	$1.29*10^{13}$
Left ventral temporal-occipital cortex (VTOC) (fusiform gyrus)	.667	.18	22.54	<.001	−44	−62	−8	$4.39*10^{19}$
Supplementary motor area (SMA)	.646	.24	16.49	<.001	−6	8	62	$2.14*10^{15}$
Right dorsolateral prefrontal cortex	.424	.30	8.55	<.001	36	26	42	$3.18*10^{7}$
Right premotor cortex	.514	.27	11.47	<.001	42	26	18	$5.34*10^{10}$
Right parietal cortex	.386	.29	8.19	<.001	52	−40	46	$1.19*10^{7}$
Right VTOC (fusiform gyrus)	.616	.20	18.79	<.001	36	−52	−8	$1.27*10^{17}$

Table 3 – Neural representational similarity (NRS) between numbers and letters in the passive fMRI task.

ROI	Mean	SD	t	p	x	y	z	Bayes Factor
Literature-based ROIs								
Number form area (NFA) (Yeo et al., 2017)	.070	.27	1.48	.15	52	−47	−18	.48
Visual word form area (VWFA) (Chen et al., 2019)	.096	.37	1.60	.12	−45	−57	−12	.56
Left intraparietal sulcus (IPS) Yeo et al. (2017)	−.031	.33	−.58	.56	−38	−46	38	.21
Right IPS (Yeo et al., 2017)	.054	.36	.92	.37	39	−52	48	.26
Whole-brain NRS-based ROIs								
Left dorsolateral prefrontal cortex	.007	.37	.11	.91	−48	24	28	.18
Left parietal cortex (IPS)	.007	.31	.13	.90	−32	−54	48	.18
Left ventral temporal-occipital cortex (VTOC) (fusiform gyrus)	.160	.36	2.72	.01	−44	−62	−8	4.16
Supplementary motor area (SMA)	−.013	.31	−.25	.8	−6	8	62	.18
Right dorsolateral prefrontal cortex	.004	.28	.06	.94	36	26	42	.18
Right premotor cortex	.002	.34	.04	.97	42	26	18	.18
Right parietal cortex	.043	.35	.76	.45	52	−40	46	.23
Right VTOC (fusiform gyrus)	.143	.32	2.76	.01	36	−52	−8	4.52

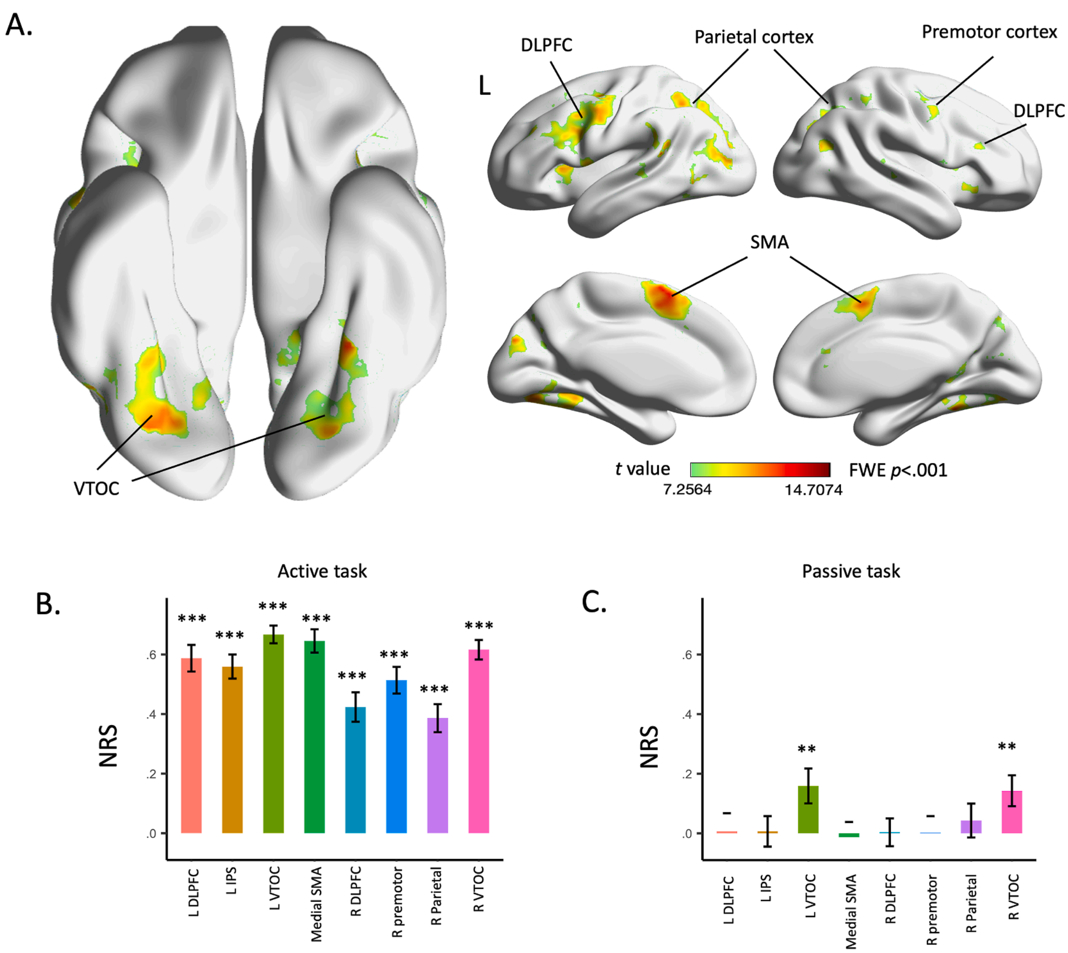

Fig. 4 – Neural representational similarity (NRS) reveals shared neural representations between numbers and letters in the ventral temporal-occipital cortex (VTOC) in active and passive fMRI tasks. (A) *Whole-brain NRS analysis*. In the active fMRI task, NRS between numbers and letters was significant in the bilateral VTOC as well as dorsolateral prefrontal cortex (DLPFC), premotor cortex, and parietal cortex and the supplementary motor area (SMA) (see also Table 1). In the passive fMRI task, no brain region showed significant NRS between numbers and letters from the whole brain analysis at the same statistical threshold as the active fMRI task (see also *Results*). (B) *NRS between numbers and letters in selected regions of interests (ROIs) in the active task*. High levels of NRS between numbers and letters were observed in multiple brain regions in the active fMRI task. (C) *NRS between numbers and letters in selected ROIs in the passive task*. In the passive fMRI task, among the same set of ROIs examined as the active dataset, only the bilateral fusiform gyrus in the VTOC showed significant NRS between numbers and letters. L = left; R = right; $^{**}p < .01$, $^{***}p < .001$.

We first performed the ND-EN analysis in the active task. Here, we found that the classification accuracy (78.38%) was statistically significant based on permutation testing ($p < .001$, with 5000 iterations of permutation). The regularization procedure revealed that 3.14% (927 voxels) of the total voxels had nonzero weights. These voxels spanned multiple clusters in prefrontal, parietal, and visual cortices, which jointly contributed to successful classification (Table 1 and Fig. 2A). We then obtained the mean feature importance from 6-mm spherical ROIs centered on the peak coordinates of all identified clusters. Among all the ROIs, the thalamus, left fusiform, left lateral occipital and visual cortices, left premotor cortex and primary sensory cortex, right IPS, right lateral occipital cortex, right superior temporal gyrus, right inferior frontal gyrus (BA 44) and anterior prefrontal cortex are the regions that showed relatively higher importance features in the collection of brain regions that survived the regularization (Fig. 2B, see also Table 1).

We additionally examined feature importance in literature-based ROIs (Fig. 3A) and assessed statistical significance using permutation tests. Here, only the VWFA ROI from Chen et al. (Chen, Wassermann et al., 2019) showed significantly high feature importance ($p = .02$), which suggests a role for the VWFA as part of a network of brain regions including prefrontal, parietal, and visual cortices in category-sensitive representation of visual symbols. Together, our ND-EN analysis in the active task demonstrates that decodability between numbers and letters is based on multivariate patterns of activation in distributed brain regions.

3.4. ND-EN of numbers and letters in the passive task

To determine whether the patterns of distributed neural differentiation between numbers and letters are similar or different without attention allocated to visual symbols, we applied our whole-brain ND-EN analysis to the passive task. This analysis yielded no significant classification between numbers and letters (*decoding accuracy* = 58.11%, *permutation* $p = .20$), which suggests that tasks with high, but not low, cognitive demand may elicit category-sensitive distributed neural representation of visual symbols. Additionally, the GLM in the passive task yielded no significant clusters in the digit > letter + scrambled digit + scrambled letter contrast, which is consistent with the finding reported in the original paper (Merkley, Conrad et al., 2019).

3.5. Neural representational similarity (NRS) between numbers and letters in the active task

Our next goal was to examine the similarity in the neural representation between numbers and letter. Previous studies have argued that the putative NFA is engaged in differentiating numbers and letters when attention is paid to numbers or letters. However, we did not find strong evidence supporting the involvement of the NFA in decoding between numbers and letters in our study. Therefore, we examined NRS between numbers and letters in ROIs drawn from the extant literature, including the NFA (Yeo, Wilkey et al., 2017) and VWFA (Chen, Wassermann et al., 2019) (Fig. 3A). Both p values and *Bayes Factors* (*BFs*) suggest high levels of NRS between numbers and letters in these literature-based ROIs ($r = .36$, $p < .001$, $BF > 100$ for NFA; $r = .60$, $p < .001$, $BF > 100$ for VWFA; Table 2 and Fig. 3B). In addition, we examined the similarity in bilateral intraparietal sulcus (IPS) regions (Yeo, Wilkey et al., 2017), which are consistently implicated in numerical cognition (Butterworth & Walsh, 2011; Piazza & Eger, 2016). The p values and *BFs* indicate high NRS between numbers and letters in the IPS ($r = .41$, $p < .001$, $BF > 100$ for left IPS; $r = .52$, $p < .001$, $BF > 100$ for right IPS; Table 2 and Fig. 3B).

Finally, to examine whether visual numbers and letters are represented similarly in other brain regions, we conducted a whole-brain NRS analysis (see **Methods** for details) in search of regions that show overlapping neural representations between numbers and letters during the active task. Here we found significant NRS between numbers and letters in the bilateral VTOC as well as the bilateral frontal, predominantly in the left hemisphere, and parietal regions ($rs = .39–.67$; $ps < .001$, $BFs > 100$; Table 2 and Fig. 4A–B; see S2 Table for all significant clusters observed from the NRS analysis).

3.6. NRS between numbers and letters in the passive task

To investigate whether the patterns of overlapping neural representations between numbers and letters are similar or different under passive task conditions, we then performed regional NRS analysis on the literature-based ROIs. The results revealed no significant NRS between numbers and letters in these ROIs based on p values ($rs < .08$, $ps > .11$; Table 3 and Fig. 3C) during the passive task. However, the *BF* values for NRS between numbers and letters in NFA and VWFA ranged between .40 and .56, which suggests that non-significant findings from these regions ($ps > .11$) may be inconclusive (i.e., *BF* between .33 and 3).

At the whole brain level, we did not observe any cluster with significant NRS between letters and numbers ($p < .01$, FDR-corrected). At uncorrected statistical threshold, we found significant NRS between numbers and letters in the right VTOC ($p < .001$, uncorrected). To further examine whether similar representation of numbers and letters in the VTOC is modulated by task demands, we examined NRS between numbers and letters during the passive task in the ROIs derived from whole brain NRS analysis in the active task (Fig. 4A). Among these ROIs, the bilateral VTOC showed high levels of NRS based on both p values and *BFs* (left VTOC: $r = .15$, $p = .01$, $BF = 4.16$; right VTOC: $r = .14$, $p = .009$, $BF = 4.52$; Table 3 and Fig. 4C). No significant NRS was observed in other ROIs derived from the active task ($rs < .042$, $ps > .45$, $BFs = .18–.23$). These findings point to significant overlap in neural representation across numbers and letters in the VTOC during the passive task.

3.7. ND-EN and NRS of numbers and letters in age-matched cohorts in active and passive tasks

To address potential concerns about significant difference in age observed in the two cohorts of participants [active task: $n = 37$; 18.5 ± 1.5 years; passive task: $n = 37$; 25.1 ± 5.9 years; $t(1,72) = 6.57$, $p < .001$], we conducted additional analyses on age-matched subset of participants [active task: $n = 25$; 19.2 ± .8 years; passive task: $n = 15$; 18.5 ± 1.5 years; t

(1,20) = 2.09, p = .06], and repeated the ND-EN and NRS analyses in the age-matched sample. Findings from this analysis replicated the main findings from the original sample (see Supplementary Results and S1 Fig.), which suggests that these findings were not driven by developmental differences.

3.8. *Forward meta-analysis of brain regions associated with number and letter processing*

Next, we performed a series of meta-analyses (see **Methods**), which investigated the strength of association between *digit* (but not *letter*) or *letter* (but not *digit*) and each voxel in the brain. We used top 5% probability as the threshold for identifying clusters significantly associated with *digit* or *letter*. No VTOC cluster appeared in the search of *digit* but not *letter* (Fig. 5A; S3 Table). Instead, bilateral IPS, inferior frontal gyrus/BA44, and insula, and medial frontal cortex (premotor/motor cortex) were strongly associated with *digit* but not *letter*. These results are consistent with findings from previous meta-analysis (Martin, Schurz et al., 2015; Arsalidou, Pawliw-Levac et al., 2018; Hawes, Sokolowski et al., 2019; Murphy, Jogia et al., 2019). In the search of *letter* but not *digit*, we found that the left inferior frontal gyrus/BA 44 and IPS, and VWFA and medial frontal cortex (premotor/motor cortex) were strongly associated with *letter* but not *digit* (Fig. 5B; S4 Table). Together, our forward meta-analyses identified distributed prefrontal and parietal cortical regions associated with category sensitivity for number and letter processing.

3.9. *Reverse meta-analysis of cognitive functions associated with the VTOC and its subdivisions*

Finally, we investigated the brain regions associated with number and letter processing based on 14,371 published fMRI studies and 89 cognitive atlas terms (Poldrack, Kittur et al., 2011) in the Neurosynth database (Yarkoni, Poldrack et al., 2011). We performed a series of reverse meta-analyses (see also **Methods**) by assessing terms most likely associated with the VTOC and its subdivisions, NFA and VWFA, using NeuroLang, a probabilistic logic language (https://neurolang.github.io, Iovene & Wassermann, 2020). We tested the probability of each term being associated with bilateral VTOC, NFA, and VWFA ROIs (see also **Methods**; Fig. 6A–B; S5-S8 Tables). We used top 5% as the threshold for determining whether a term is significantly associated with a region. We found *face recognition* to be a term associated with both left and right VTOC and NFA. *Object recognition* and *navigation* were among terms associated with both left and right VTOC. *Facial expression* was a term associated with both right VTOC and NFA. *Word recognition* was a term associated with both VWFA and NFA. *Reading* was a term associated with both left VTOC and VWFA. Importantly, we did not find *digit* or *letter* appearing as terms

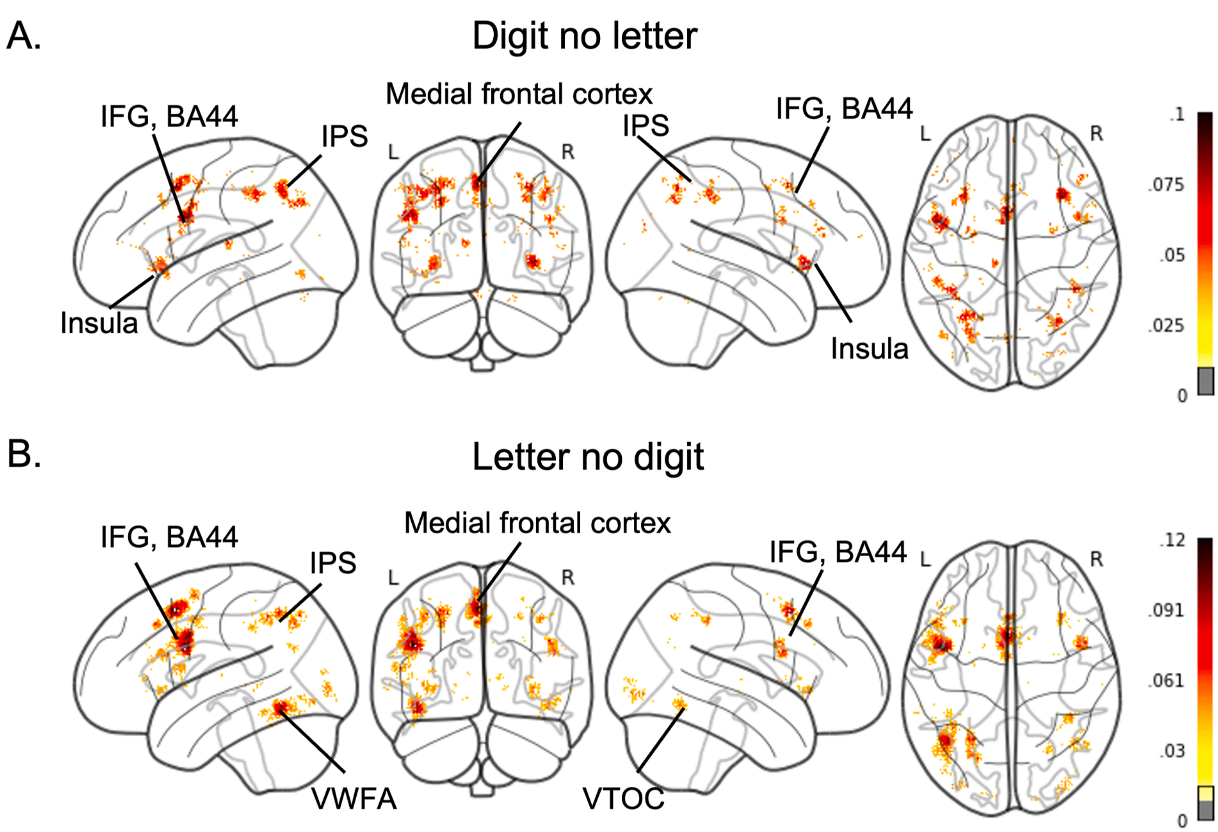

Fig. 5 – Forward meta-analysis yielded distributed neural systems associated with digit (but not letter) and*letter (but not digit*). (A) Meta-analysis of *digit* (but not *letter*) revealed a network including bilateral intraparietal sulcus (IPS), inferior frontal gyrus (IFG)/BA44, and insula, and medial frontal cortex. Notably, no VTOC subdivision was observed. (B) Meta-analysis of *letter* (but not *digit*) yielded canonical language areas in the left hemisphere, including the left IFG/BA44 and IPS and visual word form area (VWFA) and medial frontal cortex. L = left; R = right. Top 5% clusters associated with the given term are shown.

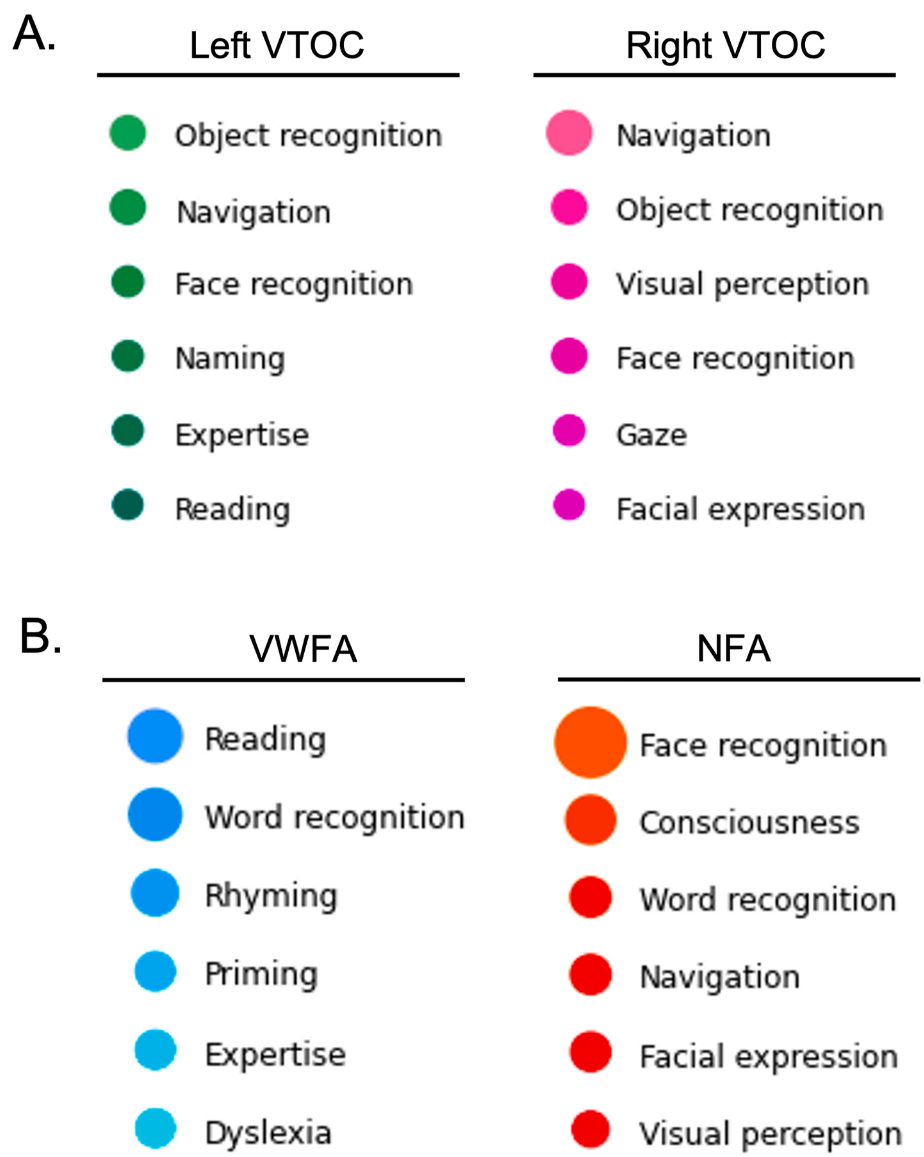

Fig. 6 – Reverse meta-analysis identifies multiple cognitive functions associated with the ventral temporal-occipital cortex (VTOC). (A–B) *Digit* or *letter* did not appear in (A) VTOC regions of interest (ROIs) that showed significant neural representational similarity between number and letters in active fMRI task (Fig. 4A) or (B) number form area (NFA) or visual word form area (VWFA) ROI (Fig. 3A). VTOC subdivisions were broadly involved in visual perception, including *face recognition* (left and right VTOC and NFA), *object recognition* (left and right VTOC), and *word recognition* (NFA and VWFA), and other cognitive processes, including *navigation* (left and right VTOC) and *reading* (left VTOC and VWFA). The radius of each circle represents the log odds ratio between the probability of a cognitive atlas term appearing in a study where the ROI appeared and the probability of the term not being mentioned in a study where the ROI was mentioned. Top 5% of all the terms associated with the given ROI are shown.

associated with left or right VTOC, VWFA, or NFA. Instead, our reverse meta-analyses revealed that multiple cognitive functions were associated with the VTOC and its subdivisions, indicating lack of category sensitivity for numbers or letters.

4. Discussion

We combined experimental research and meta-analyses to address outstanding questions related to category sensitivity for numbers and letters in the human brain. Utilizing multivariate neural pattern analysis, we investigated how category-sensitive representations of these symbols are distributed across the brain and examined the role of task level engagement in modulating this sensitivity. Brain-wide neural decoding using Elastic Net (ND-EN) revealed distinct neural representations for numbers and letters in multiple distributed brain regions under conditions where attention was actively directed towards these symbols. Such differentiation was not evident during passive viewing. Additionally, regional neural representational similarity (NRS) analysis revealed that subregions within the bilateral fusiform gyrus in VTOC displayed similar patterns of representation for numbers and letters, in both tasks. These empirical findings were further corroborated by our quantitative meta-analyses of an extensive body of fMRI studies, which confirmed involvement of the distributed brain regions in the processing of numbers and letters. Our comprehensive approach signifies a departure from the previous emphasis on specific areas within the VTOC. Our findings suggest a more intricate and interconnected framework of neural representations, emphasizing the significance of considering multiple brain regions in processing of numbers and letters. This insight could potentially reshape our comprehension of how the brain orchestrates the processing of fundamental visual symbols.

4.1. *Whole-brain decoding of numbers and letters*

The primary goal of the empirical research component of our study was to determine the involvement of distributed brain regions in the categorical representation of numbers and letters.

To achieve this, we utilized brain-wide ND-EN analysis to assess the relative contribution of each brain voxel to the discriminability between numbers and letters across two different tasks. Unlike other searchlight-based approaches, the ND-EN analysis allowed for the examination of voxels across the entire brain simultaneously. This enabled the identification of regions with the highest importance, while also accounting for contributions from the rest of the brain.

In the active task, we found that a network encompassing the ventral and dorsal visual pathways, along with the dorsolateral prefrontal cortex and insula, jointly contributed to the differentiation between numbers and letters (Fig. 1). Several areas demonstrated high contributions to the brain-level decoding of numbers and letters during this task. Specifically, this included the left fusiform gyrus, known for its involvement in processing visual words and forms (Dehaene & Cohen, 2011), and areas within the lateral occipital cortex, which are implicated in visual object recognition (Grill-Spector, Kourtzi et al., 2001; Kourtzi & Kanwisher, 2001). Intriguingly, the putative number form area, which has been reported to be specifically associated with numerical processing, did not show significant contribution to this differentiation. This suggests engagement of multiple VTOC regions in active processing and categorization of these symbols, rather than localization to a specific isolated subdivision.

In addition to the ventral visual pathway, our brain-wide ND-EN analysis also revealed involvement of the right intraparietal sulcus (IPS), a key component of the dorsal visual pathway, in differentiating between numbers and letters. This finding aligns with the role of the IPS in visual representation of numbers, and its connectivity with the ventral visual pathway (Uddin, Supekar et al., 2010; Lerma-Usabiaga, Carreiras et al., 2018; Chen, Wassermann et al., 2019). The IPS is recognized as a critical hub for manipulating numerical quantity (Butterworth & Walsh, 2011; Piazza & Eger, 2016) and it plays a role in spatial attention and working memory (Szczepanski, Konen et al., 2010; Rottschy, Langner et al., 2012; Bray, Almas et al., 2015; Mackey & Curtis, 2017, Liu, Pinheiro-Chagas et al., 2021; Menon & Chang, 2021). This observation of IPS involvement reinforces the notion that understanding the neural processing of numbers and letters requires considering both the ventral and dorsal visual pathways and their interconnections.

Notably, brain-wide ND-EN also revealed that the right DLPFC, BA44, premotor area, and insula contributed to whole-brain decoding of numbers and letters. This finding aligns with previous meta-analyses that have highlighted the involvement of the prefrontal cortex and insula in a wide range of number-related tasks (Arsalidou & Taylor, 2011, Sokolowski, Fias et al., 2017; Yeo, Wilkey et al., 2017). Additionally, evidence from single-cell recordings in non-human primates also supports this finding, showing that prefrontal neurons are sensitive to numerical quantities (Nieder & Dehaene, 2009; Nieder & Miller, 2004; Viswanathan & Nieder, 2013). This finding of the prefrontal cortex contributing to decoding numbers and letters indicates a higher level of semantic processing for symbolic numbers, compared to individual letters (as compared to words), which typically lack a similar depth of semantic representation, during the active task.

In contrast to the active task, there were no neural features that jointly distinguished between numbers and letters in the passive task. These findings suggest that neural differentiation between numbers and letters is facilitated by a distributed network and is influenced by task engagement. Consistent with previous suggestions that attention may enhance category sensitivity (Culham, Cavanagh et al., 2001; Murray & Wojciulik, 2004; Vogel, Petersen et al., 2014; Chen, Wassermann et al., 2019; Pollack & Price, 2019), our findings indicate that task level engagement plays a key role in how the brain processes and differentiates the categories of visual symbols.

4.2. *Neural representations in individual VTOC and parietal cortical regions*

To complement and extend findings from the brain-wide neural decoding we utilized neural representational similarity (NRS) analysis to probe neural representations of numbers and letters within the VTOC and parietal cortical regions of interest (Fig. 3). NRS is particularly well suited for examining subtle yet significant differences in neural representations at a fine spatial scale in individual brain areas (Kriegeskorte, Mur et al., 2008; Diedrichsen & Kriegeskorte, 2017). We adopted both ROI-based and whole-brain searchlight approaches to examine the neural representational similarities in subregions of the VTOC, IPS, and across the whole brain.

Our NRS analysis revealed a significant overlap in neural representations between numbers and letters in several VTOC regions for both active and passive tasks. The overlap was more pronounced in subdivisions of the VTOC in the active task compared to the passive task. The subdivisions of the VTOC, which include the visual word form area (Dehaene & Cohen, 2011, Chen, Wassermann et al., 2019) and the putative number form area (Grotheer, Herrmann et al., 2016; Yeo, Wilkey et al., 2017), have been previously implicated in category sensitivity for numbers and letters. However, Bayes Factor analysis revealed stronger evidence for shared neural representation between numbers and letter in subdivisions in bilateral fusiform gyrus than in the visual word form area and number form area. Our findings suggest that, rather than being highly specific to one category, individual VTOC regions are similarly responsive to numbers and letters. This observation complements our brain-wide decoding analysis using ND-EN, in which found that the preference for numbers during active tasks is not confined to isolated VTOC regions. Crucially, the visual word form area, putative number form area, and fusiform gyrus all emerged as part of a distributed system, rather than acting in isolation for differentiating between numbers and letters. Additionally, analysis using VTOC, IPS, and angular gyrus ROIs based on the triple-code model of numerical cognition (Cohen & Dehaene, 1995, Piazza, Pinel et al., 2007; Yeo, Wilkey et al., 2017; Sokolowski, Matejko et al., 2023) did not reveal distinct category-specific patterns for numbers versus letters (see Supplementary Results, S3 Fig). These findings suggest that the neural representation of numbers and letters may be more widely distributed and less constrained to regions proposed by the triple-code model.

In summary, our comprehensive neural pattern analysis reveals that individual VTOC subdivisions respond to both numbers and letters without a strong preference for one category over the other. In line with previous research and meta-analyses (Pollack & Price, 2019; Price & Ansari, 2011; Yeo, Wilkey et al., 2017; Grotheer, Jeska et al., 2018; Merkley, Conrad et al., 2019), our study highlights the importance of considering both brain-wide and region-specific approaches to better understand the neural representation of visual symbols.

4.3. *Why category representation of numbers and letters differs at the brain-wide level*

Although numbers and letters may appear visually similar as single characters, they serve distinct cognitive roles. Numbers inherently represent quantities, whereas individual letters do not carry intrinsic meaning by themselves. These fundamental differences were evident in both behavioral performance and neural processing in the active task of our study. Behaviorally, participants demonstrated faster and more accurate responses when processing numbers as compared to letters. This suggests that numbers, likely due to their quantitative and more semantic nature, may engage deeper encoding than letters. Numbers may activate semantic associations by representing specific quantities, whereas letters may require contextualization within words to gain meaning. The observed performance advantage of numbers compared to letters align with the level of processing principle that semantically encoded materials are processed more deeply and are better remembered than perceptually encoded materials (Craik & Tulving, 1975; Neely, 2012).

From a neural perspective, our whole-brain ND-EN analysis revealed a distributed system encompassing prefrontal, parietal, and visual cortices that differentiated between numbers and letters during the active task. This finding indicates that when participants are actively engaged with the symbols, different sets of brain regions are recruited to process their distinct cognitive aspects: numbers being tied to quantities may activate a semantic network, and letters being part of a more abstract, less semantic symbolic system. The differential involvement of widespread brain regions suggests that the brain leverages different cognitive resources, such as more semantic processing for numbers, compared to letters, to facilitate efficient differentiation between the two categories.

In contrast, in the passive task, when participants were not explicitly directed to actively process the symbols, numbers and letters were processed indistinguishably at the neural level. This finding suggests that, in the absence of active engagement, the difference in semantic depth between numbers and letters may have been reduced, resulting in a more generalized and indistinguishable neural representation of symbols. The lack of neural differentiation between numbers and letters in the passive task highlights the critical role of active task engagement in modulating how the brain processes and distinguishes between these two categories of visual symbols. Together, these findings suggest that task-level engagement may influence the brain's ability to differentially process numbers and letters.

4.4. *Convergent findings from probabilistic meta-analysis*

The second aspect of our two-pronged approach involved quantitively rigorous meta-analyses to systematically evaluate regional and distributed category sensitivity for numbers and letters. We utilized NeuroLang, which is a powerful tool for neuroimaging meta-analysis (Iovene & Wassermann, 2020). This innovative meta-analytic approach provides probabilistic estimations of brain activation at voxel level given cognitive terms of interest, or vice versa, the probability of terms of interest associated with brain activations at voxel level. In addition, NeuroLang allows for conditional estimation that enables a more precise examination of the association between brain activations and cognitive terms.

Using NeuroLang (Iovene & Wassermann, 2020), we first conducted a series of forward meta-analysis, in which we sought to identify brain regions differentiating numbers and letters across 14,371 fMRI studies in the Neurosynth database (Yarkoni, Poldrack et al., 2011). These conditional meta-analyses identified brain regions associated with numbers but not letters, while ruling out studies in which both terms occurred. Our findings revealed that number processing preferentially activated bilateral parietal and prefrontal cortices and the insula, aligning with previous studies in numerical cognition (Piazza, Pinel et al., 2007; Rusconi, Bueti et al., 2011; Sokolowski, Fias et al., 2017). Notably, no VTOC region was found to be specifically associated with numbers as opposed to letters. The processing of letters was more consistently associated with canonical language-related areas in the left hemisphere, including the visual word form area and the pars opercularis subdivision of the inferior frontal gyrus (BA44).

We next conducted a series of reverse meta-analysis across 14,371 fMRI studies and 89 cognitive atlas terms (Poldrack, Kittur et al., 2011) in Neurosynth database (Yarkoni, Poldrack et al., 2011). These reverse meta-analyses determined cognitive functions that were most likely associated with individual brain regions. We utilized these meta-analyses to confirm whether the VTOC regions identified from the NRS between numbers and letters in the current study, as well as visual word form and putative number form subdivisions, were responsive to a wide range of visual categories in previous literature. Our findings indicated that these VTOC regions did not show a specific preference for numbers or letters, but rather were associated with various types of visual perception, including face recognition, object recognition, and word recognition, and other cognitive processes such as navigation and reading. This suggests that the role of VTOC is not exclusive to numbers or letters but extends to a broader array of cognitive functions.

Taken together, our meta-analytic findings, along with results from multivariate ND-EN and NRS analysis, indicate that cognitive processing associated with numbers and letters is supported by multiple distributed brain regions. These results suggest that the VTOC has a more generalized role in perceptual and cognitive processes and emphasize the importance of distributed neural systems in category-sensitive processing of numbers and letters.

4.5. *Overlapping brain regions in number and letter processing: subregional and voxel-level differentiation*

It is worth noting that our forward meta-analysis revealed that several brain regions, including the IPS and IFG, were associated with both numbers and letters, which may appear counterintuitive for meta-analyses involving the search of "digit but not letter" and "letter but not digit". There are several plausible explanations for this finding.

First, different subregions within these broader areas were selectively involved in processing numbers and letters. For example, the IPS and IFG are large, functionally diverse regions that have been implicated in multiple cognitive tasks. Functional differentiation within these regions could allow for distinct subregions to specialize in either numbers or letters, even though both categories may recruit the same broader region. This functional specificity within subregions could explain the apparent overlap in brain areas supporting both types of symbolic processing. Second, within the same general brain region, voxel-level distinctions in neural activity could lead to different patterns of activation for numbers and letters. This voxel-level differentiation may contribute to category-sensitive neural representations, while allowing shared anatomical regions to support distinct cognitive processes.

In sum, while some brain areas may be involved in processing both numbers and letters, the selectivity for each category might emerge through finer-grained neural mechanisms at the subregional or voxel level. In the current study, multivariate approaches enabled us to capture the nuanced ways in which the brain represents different categories of visual symbols.

4.6. *Limitations and future directions*

Several limitations of our study warrant consideration. One limitation of our study is that the active and passive tasks were conducted with different participant cohorts, precluding a direct within-subject comparison across task contexts. To address this issue, we conducted additional analyses in an age-matched subset of participants (see *SI* Results). The replication of key findings suggests that our results are robust and not primarily driven by developmental differences. However, other individual differences, such as variations in math and reading abilities, could also influence neural representations of numbers and letters. While the active task cohort exhibited math and reading abilities within the normative range, similar data were not available for the passive task cohort. Although the passive cohort was not recruited from an atypically developing population, the lack of direct behavioral assessments introduces some uncertainty. Future studies should incorporate within-subject experimental designs to examine how neural representations of visual symbols change as a function of task engagement and attentional demands. Additionally, assessing individual differences in numerical and reading expertise could provide further insight into how learning history influences distributed neural coding of symbolic representations.

Another limitation is that the findings from our reverse meta-analysis may be influenced by biases in the existing literature. Specifically, more frequently studied topics – such as object and face recognition – are more likely to appear in large-scale meta-analyses than number and letter processing. As a result, our reverse meta-analysis findings do not entirely rule out the possibility of number- or letter-sensitive subregions in the VTOC. Instead, they highlight the general role of the VTOC in visual object processing and align with our NRS findings, which showed similar neural representations for numbers and letters in this region. The inconsistency in the reported location of the putative number form area across studies (Yeo, Wilkey et al., 2017) and the widely distributed nature of letter representations in the VTOC (Lochy, Jacques et al., 2018) raise questions about the existence of highly localized category-specific processing in these regions. Future meta-analyses that balance the representation of different visual categories in the literature may help determine whether specific subdivisions of the VTOC are preferentially involved in number or letter processing.

Beyond these methodological considerations, future work should explore the dynamic interactions among the distributed neural systems supporting category-sensitive processing of numbers and letters. Functional and effective connectivity analyses could reveal how brain regions identified in our study work in concert to differentiate between symbolic categories under varying task demands. Additionally, longitudinal studies tracking expertise development in numerical and literacy skills could provide valuable insights into how distributed neural representations emerge and evolve over time.

5. Conclusion

Our study utilized advanced brain-wide decoding techniques, yielding convergent evidence that underscores the distributed nature of category sensitivity for numbers and letters within the human brain. Importantly, our findings underscore that this sensitivity is not confined to isolated regions but involves a distributed brain network whose engagement is modulated by task level engagement. Integrating results from multiple analysis approaches, varying task contexts, and meta-analyses of existing literature, our research provides a comprehensive view of neural processing of visual symbols. We identified that frontal and parietal cortical regions, in conjunction with the VTOC and adjacent lateral occipital cortex, play a pivotal role in the category-sensitive representation of these symbols. Notably, this joint decoding of numbers and letters across multiple brain regions was most pronounced in tasks requiring focused attention on these symbols. Our findings highlight context-sensitive and dynamic nature of neural representations of numbers and letters, emphasizing the role of distributed brain areas in processing these fundamental cognitive elements. Future research should aim at unraveling the interactive dynamics of brain regions leading to the emergence of distributed neural representations.

CRediT authorship contribution statement

Ruizhe Liu: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Hyesang Chang:** Writing – review & editing, Conceptualization. **Dawlat El-Said:** Project administration, Data curation. **Demian Wassermann:** Software, Resources, Methodology. **Yuan Zhang:** Methodology, Formal analysis. **Vinod Menon:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Code availability statement

All code is shared via the Stanford Cognitive & Systems Neuroscience Laboratory Github webpage (https://github.com/scsnl/Liu_etal_Cortex_Distributed_number_letter_2024/tree/main).

Data availability statement

Data from the passive task are available at OpenNeuro (https://openneuro.org/datasets/ds002033/versions/1.0.0). For the active task, the conditions of our ethics approval do not permit public archival of raw MRI data. However, de-identified behavioral data and functional MRI contrast images necessary to reproduce study findings are available at OSF (https://osf.io/nbemh/?view_only=069e5c83cfee4a3496a095193d6f8b2a).

Transparency and openness promotion guidelines statement

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. Study procedures and analyses were not pre-registered prior to the research being conducted.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare no usage of generative AI in the writing process.

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Declaration of competing interest

None.

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Scientific transparency statement

DATA: Some raw and processed data supporting this research are publicly available, while some are subject to restrictions: https://osf.io/nbemh/, https://openneuro.org/datasets/ds002033/versions/1.0.0, https://neurosynth.org/, https://github.com/scsnl/Liu_etal_Cortex_Distributed_number_letter_2024/tree/main.
CODE: All analysis code supporting this research is publicly available: https://github.com/scsnl/Liu_etal_Cortex_Distributed_number_letter_2024/tree/main.
MATERIALS: Some study materials supporting this research are publicly available, while some are subject to restrictions: https://github.com/scsnl/Liu_etal_Cortex_Distributed_number_letter_2024/tree/main.
DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.
PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.
For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

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