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Working memory representation of empty sets in the primate parietal and prefrontal cortices



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ABSTRACT

For the brain, representing empty sets as a precursor to zero is a challenge because it requires the active coding of a quantitative category that, by definition, contains no items. Recent neurophysiological recordings show that empty sets are distinctively encoded by neurons in the primate ventral intraparietal area (VIP) and the prefrontal cortex (PFC). However, how empty sets are represented in working memory is unknown. We simultaneously recorded from VIP and PFC while rhesus monkeys performed a delayed numerosity matching task that required the maintenance of numerosities in memory for a brief period. Countable numerosities (1–4) and empty sets ('numerosity 0') were included as stimuli. Single neurons in PFC, and to a lesser extent neurons in VIP, actively encoded empty sets during the delay period. In both cortical areas, empty sets were progressively differentiated from countable numerosities with time during the ongoing trial. Moreover, the tuning of neuron populations in VIP and PFC shifted dynamically towards empty sets so that they became increasingly overrepresented in working memory. Compared to VIP, the prefrontal representation of empty sets was more stable in time and more independent of low level visual features. Moreover, PFC activity correlated better with behavioral performance in empty set trials. These findings suggest that the representation of null quantity in working memory relies more on prefrontal and less on parietal processing. Overall, our results show that empty sets are dynamically and distinctly represented in working memory.

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1. Introduction

The number of items in a set, its numerosity, is an abstract feature of collections. The countable numerosities 1 and larger correspond to real “things” which can be enumerated. Empty sets, however, are sets with no items than could be enumerated. Realizing that an empty set, numerosity zero, is still a set

is cognitive demanding because it requires abstract thinking that is detached from empirical experience (Nieder, 2016a). Only humans grasp the symbolic concept of number zero, which is a latecomer in human history (Boyer, 1944; Dantzig, 1954) and development (Merritt & Brannon, 2013; Wellman & Miller, 1986). Nevertheless, animals such as monkeys are able to represent the nonsymbolic precursors of zero, the

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empty set (Biro & Matsuzawa, 2001; Merritt, Rugani, & Brannon, 2009; Ramirez-Cardenas, Moskaleva, & Nieder, 2016). Nonhuman primates therefore offer a window of opportunity to explore the neurophysiological realization of empty sets as a precursor to zero in relation to countable numerosities.

Accumulating evidence reveals that a parieto-frontal network has a crucial role in the representation of countable numerosities. Numerosity-selective neurons found in the ventral intraparietal area (VIP) and the dorsolateral prefrontal cortex (PFC) of primates are considered as the neuronal correlate for the capacity to represent quantity (Nieder, 2016b). Numerosity-selective neurons are tuned to preferred numerosities which elicit highest discharge rates (Nieder, 2012; Nieder, Freedman, & Miller, 2002; Sawamura, Shima, & Tanji, 2002). Relative to the preferred numerosity, selective neurons show a progressive decline of activity with numerical distance, indicating that they can discriminate between numerically distant numerosities more easily than between adjacent ones. This mirrors the behavioral ‘numerical distance effect’, the finding that the greater the magnitude difference between two numerosities, the more easily they can be discriminated (Buckley & Gillman, 1974; Merten & Nieder, 2009). The neuronal distance effect is therefore a key feature expected for neurons that encode quantitative information (Nieder & Miller, 2003).

We have recently recorded from monkeys performing a numerosity matching task including empty sets and countable numerosities (Ramirez-Cardenas et al., 2016). During presentation of visual stimuli, a parieto-frontal network is involved in the encoding of empty sets as conveying a quantitative null value. At the putative input to the number network, neurons in the ventral intraparietal area (VIP) did not exhibit a strong distance effect and encoded empty sets as a category distinct from all other numerosities. A similar finding for VIP neurons has been reported in one monkey trained to perform numerical operations on visual dots (Okuyama, Kuki, & Mushiake, 2015). Thus, VIP neurons still signal the categorical presence versus absence of items during sensory input, but not yet empty sets as quantitative magnitude. In this respect, the parietal representation of empty sets differs from that of countable numerosities.

Higher up the cortical hierarchy, however, PFC neurons represented empty sets in a more graded fashion (Ramirez-Cardenas et al., 2016). PFC neurons responded more similarly to numerosity 1 than to larger numerosities, thereby exhibiting a numerical distance effect. Moreover, prefrontal neurons represented empty sets abstractly and irrespective of stimulus variations. Compared to VIP, the activity of numerosity neurons in PFC also predicted better the successful or erroneous behavioral outcome of empty-set trials. These results suggest a hierarchy in the processing from VIP to PFC, along which empty sets are progressively detached from visual properties and gradually positioned in a numerical continuum.

While these data provided insights into the sensory coding of empty sets during stimulus presentation, the working memory representations of empty sets are unknown. The delayed match-to-numerosity task we trained the monkeys to perform contained a delay period that required them to keep

numerosities in working memory. In the current paper, we therefore analyzed the sustained neuronal responses during the delay period in area VIP and PFC of behaving rhesus macaques.

2. Methods

2.1. Subjects & surgical procedures

Two adult rhesus monkeys were implanted with 2 recording chambers each, centered over the principal sulcus in the dorsolateral prefrontal cortex and the VIP in the posterior parietal cortex. The posterior and ventral parts of area 46 of the prefrontal principal sulcus receive direct input from parietal VIP (Lewis & Van Essen, 2000); no attempts have been made to differentiate between sub-regions of the prefrontal sulcal region. All procedures were performed in accordance with the guidelines for animal experimentation required by authorities (Regierungspräsidium Tübingen, Germany).

2.2. Behavioral protocol

Monkeys were trained in a delayed-match-to-sample numerosity discrimination task involving as stimuli sets of black dots (0–4) against a gray background (Fig. 1A). In order to start a trial, monkeys were required to grab a bar and keep eye fixation. Then, a green square or circle background appeared on the screen during a 500 msec ‘fixation period’. After achieving eye fixation for 500 msec, a sample numerosity was displayed in the center of the screen for 500 msec. The sample stimulus consisting of a gray background containing 0 to 4 dots. This sample period was followed by a 1-sec-delay showing a green background in which the numerosity should be maintained in working memory. Subsequently, a first test stimulus (test 1) was shown for 500 msec and monkeys were expected to release the bar during the presentation of the test stimulus if it matched the sample stimulus in quantity. That happened in half of the trials, referred as ‘match trials’. If the monkey failed to release the bar to the test1-stimulus in ‘match-trials’, a red screen was flashed as negative feedback and no reward was delivered. In the other half of the trials, a 300 msec delay (delay 2) showing a green background was followed by a second test stimulus (test 2; 500 msec duration) which always matched sample number. The monkeys were required to release the bar during presentation of the test2-stimulus in these non-match trials.

2.3. Stimuli

Stimuli were shown in the center of an LCD screen 57 cm in front of the monkey’s eyes. Numerosity stimuli consisting of multiple-dot patterns against a gray background (diameter of 5.7° visual angle) were created using custom-written Matlab software.

Two stimulus protocols were introduced to control low-level visual features. In standard trials, dot location and diameter were varied pseudo-randomly. In control trials, total dot area, dot density and total stimulus luminance were kept constant across countable numerosities (see Fig. 1B).

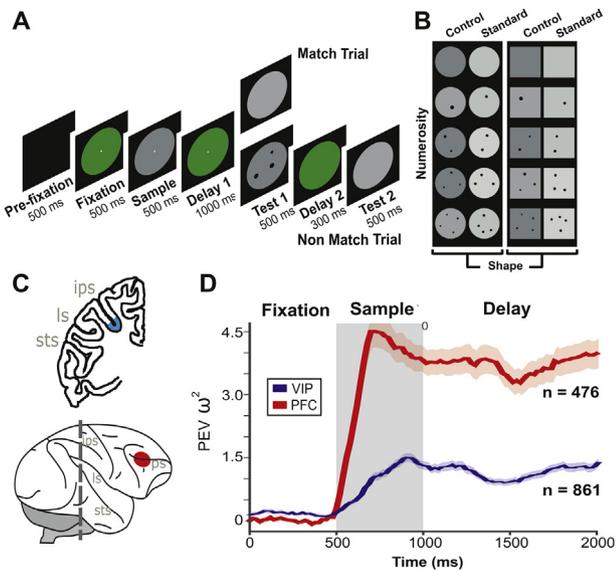


Fig. 1 – Behavioral task, stimuli, recording sites and neuronal information about numerosity. (A) Task. Monkeys were presented with a sample numerosity ranging from 0 to 4 for 500 msec. Monkeys had to keep the sample numerosity in memory for a 1-sec delay period and match it to a subsequent test stimulus (either the first or the second test stimulus) by releasing a lever. **(B) Example stimuli for the different conditions.** Empty sets (zero) and countable numerosities 1 to 4 (factor ‘numerosity’) were shown in standard and control protocols (factor ‘protocol’) on a circular or square background (factor ‘shape’). **(C) Recording sites.** Lateral view and coronal section of the right hemisphere of a monkey indicating cortical landmarks, reconstructed from a structural MRI scan. The red region on the frontal lobe and blue region in the fundus of the IPS mark the recording sites in PFC and VIP, respectively. *ips*, intraparietal sulcus; *ls*, lateral sulcus; *sts*, superior temporal sulcus. **(D) PEV (ω^2) for numerosity in the whole population of VIP and PFC neurons.** Mean percentage of firing rate inter-trial variance across neurons explained by the main factor sample numerosity during a trial.

Background luminance was systematically varied across and between protocols to control total stimulus luminance. To test how invariant the neuronal representation of empty sets is to image-like features, both stimulus protocols were shown either with a circular or a square background. Therefore, we included a total of 20 specific conditions (5 sample numerosities \times 2 types of protocol \times 2 background shapes). New stimuli sets were generated for each session using Matlab routines. To prevent the monkeys from memorizing the visual patterns of the displays, each quantity was tested with different images per session, and the sample and test displays were never identical in one trial.

2.4. Neurophysiological recordings

In each session, arrays of glass-coated tungsten microelectrodes (Alpha Omega Ltd., Israel) were inserted in each

recording chamber using a grid (Crist Instruments, USA) with 1-mm spacing. A maximum of 8 microelectrodes were used per cortical area in one session and we tried to keep the recording sites constant over sessions. Neurons were selected at random, as no attempt was made to preselect neurons according to response properties. Only stable and well isolated neurons were recorded. A MAP Plexon system was used for signal acquisition, amplification, filtering and digitalization. Waveform separation was performed off-line (Plexon Systems, USA) using principal components and other characteristics of the waveforms.

Neurons with a minimum average firing rate of 1 Hz and at least 3 stimulus repetitions per specific condition were considered for further analysis. We corroborated that our main results hold true when we increase the number of required repetitions to 5 repetitions. No attempts were made to determine the visual response fields of the neurons. In a previous publication, we analyzed responses to the sample period of the dataset (Ramirez-Cardenas, et al., 2016). In the current publication, we revisit the identical dataset but focus on the working memory period, i.e., the delay period.

2.5. Analytical methods

Epoch defined selectivity and tuning curves. Neuronal activity in response to numerosities during the delay epoch was evaluated in the 1 sec window between delay-onset and delay-offset. We run a 3-way ANOVA with factors number (5 sample numerosities), protocol (standard and control) and shape (circle and square) to determine selectivity and evaluated the significance for each factor at $p < .01$. To create single-neuron tuning curves, we first calculated per neuron the average trial firing rate for each sample numerosity (0–4) and then we normalized those mean firing rates (across numerosity classes) from 0 to 1. Finally, to obtain population tuning curves (Fig. 3A,C), we averaged the single-neuron tuning curves of neurons with the same preferred numerosity.

2.5.1. Error analysis

We compared firing rates in error and correct trials in empty set neurons with at least three non-correct trials per relevant numerical category. Only empty-set neurons with at least 3 error trials per compared stimulus category were considered in the firing rate error analysis. Furthermore, to evaluate the behavioral relevance of numerosity selective neurons regardless their number preference, we calculated ω^2 PEV for numerosity (percentage of explained variance) in sliding windows (200 msec kernel, 20 msec step) in correct and error trials. In this case, we only included those numerosity selective neurons recorded during at least two error trials per numerical category. A Wilcoxon-signed-rank test was used for statistical comparison of firing rates and PEV in correct and error trials.

2.5.2. Time-defined definition of numerosity selectivity

We used ω^2 PEV (percentage of explained variance) to assess the influence of different factors on trial firing rates. ω^2 was calculated for each neuron in a sliding window (200 msec kernel, 20 msec step) from a 3-way ANOVA with main factors number, protocol and shape. Twenty five balanced

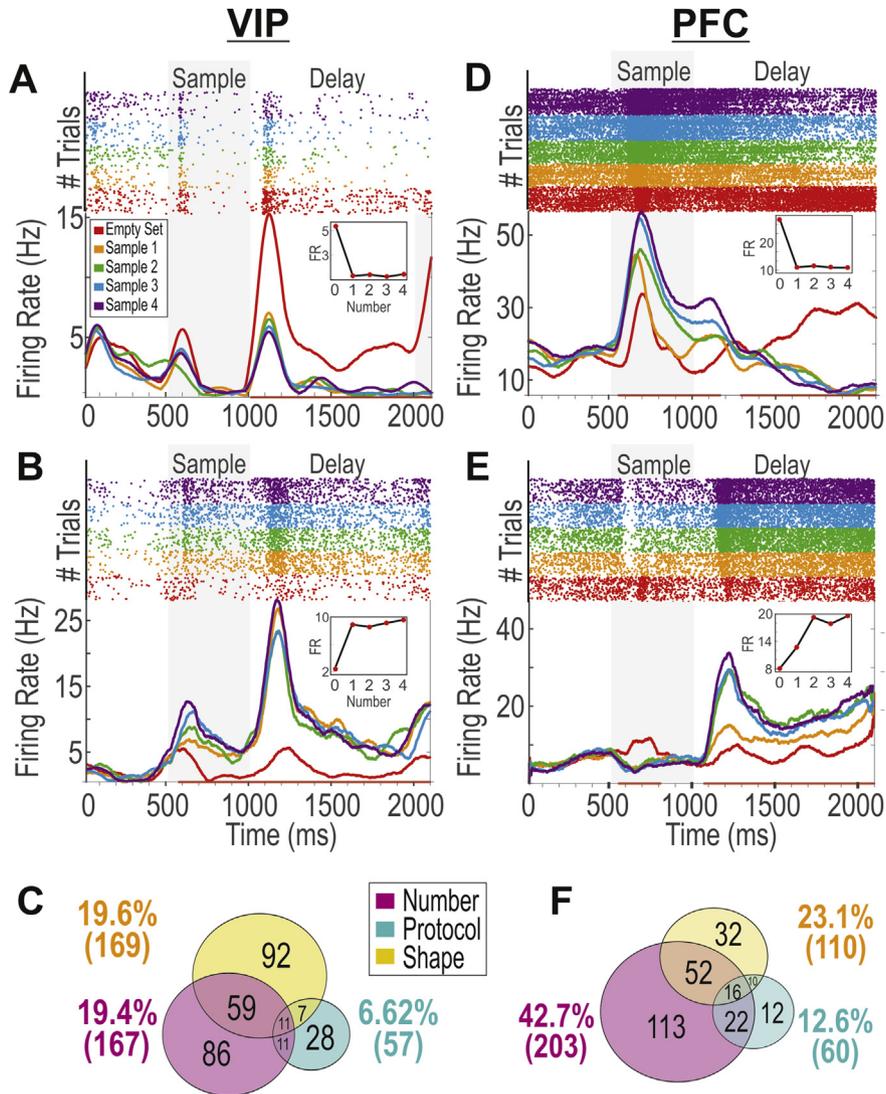


Fig. 2 – Single-neuron selectivity to numerosities 0 to 4. (A & B, D & E) Examples of single neurons with numerosity selective responses in the delay period. (A & B) Example numerosity selective neurons in VIP. Top panel shows dot-raster histograms (each dot represents an action potential); bottom panel depicts averaged spike density functions (activity averaged in a sliding 150 msec window). The first 500 msec represent the fixation period, followed by the sample (500 msec) and delay (1 sec) periods. Inset in spike density plot shows the tuning function (i.e., discharge rates as a function of the number of presented items) during the delay period. (D & E) Example numerosity selective neurons in PFC. (C & F) Single neuron selectivity for main ANOVA factors in VIP and PFC neuronal populations. Venn Diagrams depict the distribution of selectivity for the 3 main ANOVA factors (sample numerosity, protocol and shape) in VIP (Fig. 2C) and PFC (Fig. 2F) single-neuron populations during the delay period.

permutations were run and averaged to define a reference ω^2 value. For each neuron and factor, a permutation test was used to assess the significance of this value per time bin (1000 shuffles, evaluated at .01). A ‘numerosity selective response’ was defined as at least 3 consecutive bins which were significant for main factor number and not any other factor or interactions. The stringency of our criteria was confirmed by the low incidence of numerosity selective responses, so defined, during fixation in both prefrontal and parietal neurons (<1% of responses in the sample period, with the same duration). Responses are classified as sample and delay responses according to their timing.

2.5.3. Characterization of the tuning profile of empty-set preferring neurons

We fitted the tuning curve of each empty-set preferring neuron with a generalized linear model (GLM) that contained a linear combination of two regressor functions: a decreasing linear function (graded tuning) and a step-like function (categorical tuning). The graded tuning profile was modeled by a linear decreasing function:

$$fr(n) = -a*n + b;$$

While the categorical tuning profile was modeled by a step function:

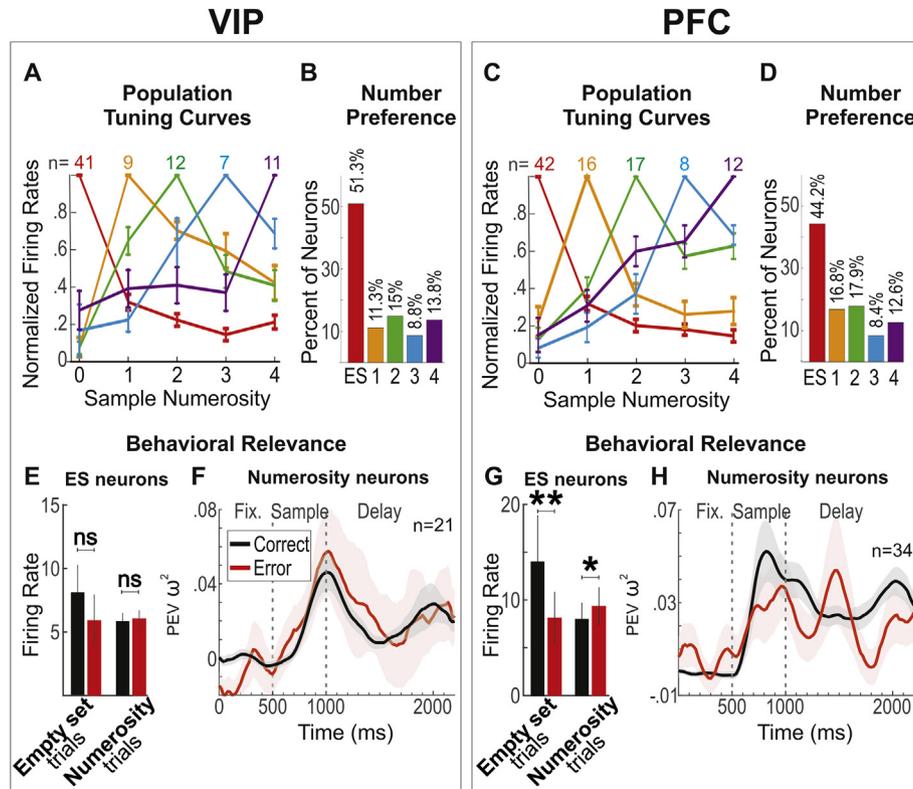


Fig. 3 – Neuronal tuning during correct and error trials. (A & C) Population tuning curves obtained by averaging the normalized tuning curves of VIP and PFC single neurons with the same preferred stimulus in the delay period. Error bars indicate the SEM. (B & D) Proportions of neurons in VIP and PFC responding maximally to different sample numerosities during the delay period. (E & G) Behavioral relevance of VIP and PFC empty set preferring neurons in empty-set trials (preferred stimulus) and in countable-numerosity trials (least preferred stimulus). The firing rates during the delay period are compared in correct (black) and erroneous trials (red). [$p < .01$, * $p < .05$]. (F & H) Behavioral relevance of VIP and PFC numerosity selective neurons. PEV (ω^2) for numerosity (from a 3-factor ANOVA) in correct (black) and error trials (red) during the sample (500–1000 msec) and delay periods (1000–2000 msec).**

$$fr(n) = \begin{cases} fr(0), & \text{if } n = 0 \\ b, & \text{if } n \geq 0 \end{cases}$$

We defined the best parameters (a and b in equations) of such functions for each tuning curve by fitting (least squares fit). Then, we applied the GLM and obtained β coefficients for each regressor. These coefficients correspond to the weight assigned to each regressor (linear or step-like function) in the GLM and therefore reflect to what extent a particular tuning curve can be described as the corresponding category (graded or categorical tuning, respectively). We used Mann–Whitney U test to compare values between different cortical areas and Wilcoxon signed rank test to compare different epochs.

2.5.4. Cross-correlation coefficients between subsequent time-defined tuning curves

Time-defined tuning functions were obtained per neuron in a sliding window of 200 msec with a step of 20 msec and normalized (from 0 to 1). Cross-correlation coefficients (CCs) between subsequent pairs of normalized time-defined tuning curves were then calculated. For a fair comparison between cortical areas we corrected CCs with respect to baseline

values, which were higher in PFC neurons than in VIP neurons. For each neuron, the mean CC during the fixation period was subtracted from the time-defined values. Then, time bin values in the relevant epochs (sample and delay) were averaged per neuron. The bar plot in Fig. 4C represents the mean corrected CCs over neurons in VIP and PFC. We used Mann–Whitney U test to compare values between different cortical areas.

2.5.5. Mean cumulative numerical shift

The preferred numerosity of time-defined tuning curves (200 msec sliding window with a 20 msec step) was identified and the difference between consecutive preferred numerosities was calculated for each neuron. Then these differences (numerical shift) were cumulatively summed per neuron. Fig. 4D shows the mean in cumulative numerical shift over parietal (blue line) and prefrontal (red line) neurons.

2.5.6. Decoding analysis

In each cortical area, we created a preference balanced pseudo-population of 150 neurons. We used a multi-class linear support vector machine (SVM) classifier (Chang & Lin, 2011). The ‘one-versus-one’ classification method was

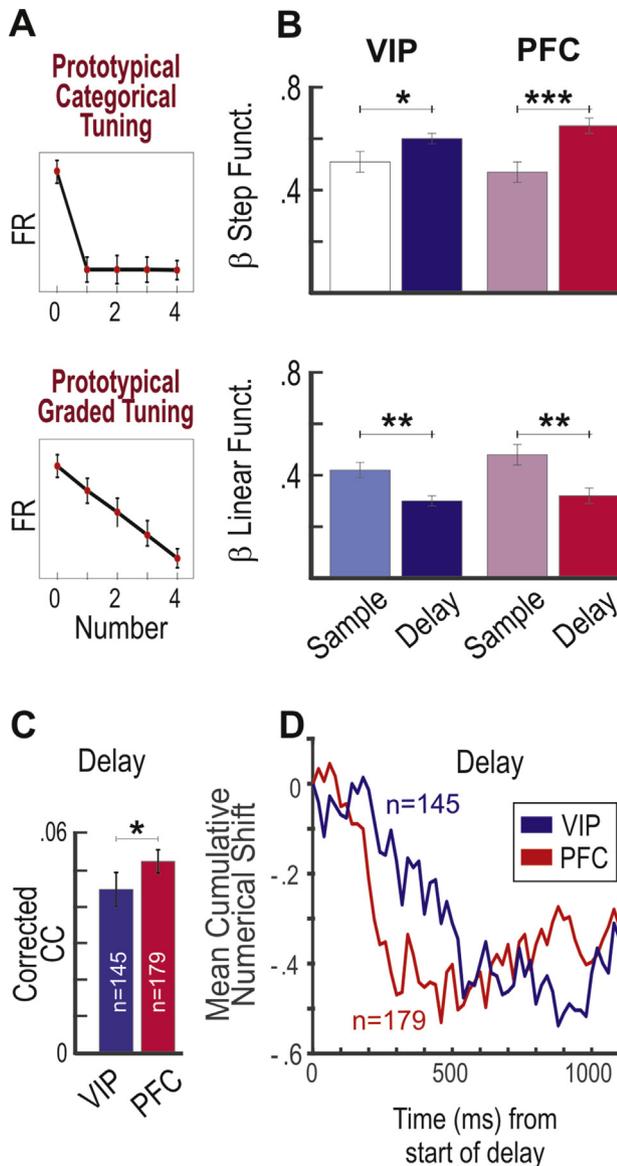


Fig. 4 – Tuning differences between VIP and PFC and their temporal evolution during the trial. (A) Categorical and graded tuning profiles for empty set preferring responses. Prototypical categorical (top) and continuous (bottom) empty-set tuning functions. (B) Fitting of empty set preferring tuning curves: The tuning curves of empty-set preferring responses were fitted with a GLM containing as regressors a step-like function and a monotonically decreasing linear function. Bars represent the mean β values assigned to each of these regressor in VIP (blue) and PFC neurons (red), during the sample and delay periods. Error bars indicate the SEM. Significance was tested with a Mann–Whitney *U*-test. [* $p < .001$, ** $p < .01$, * $p < .05$]. (C) Correlation coefficient of time defined tuning curves. For each neuron, we obtained cross-correlation coefficients between subsequent pairs of time-defined tuning curves (200 msec sliding window, 20 msec step). After correcting CCs with respect to baseline values (See methods) we calculated mean CCs over neurons in VIP and PFC. Error bars indicate the SEM. Significance was tested with a Mann–Whitney *U*-test. (D) Mean accumulated numerical**

deployed when dealing with five classes (0–4). Ten-fold cross-validation was performed using the ‘leave-one-group-out’ paradigm. The whole procedure was repeated 50 times after random resampling. We report the mean performance and standard deviation over resamples. To test the generalization across different conditions (Fig. 5H), we run the classification procedure in both directions of training and testing (for example, from circles to squares and vice versa) and report the average in the main text. To test the stability of the neural representation of numerosity we also run the classification procedure using different trial epochs for training and testing (for example, we trained the classifier with firing rates from the sample epoch and tested with activity from the delay period, and vice versa).

3. Results

We trained two monkeys in a delayed-match-to-sample task to discriminate visual numerosities 0 (i.e., empty sets) to 4 (see Fig. 1A). Low level and image-like visual features of the numerosity displays were controlled by introducing two protocol conditions (standard or control) and two shapes for the background (circle or square) (see Fig. 1B). After sample presentation, the monkeys were required to hold the displayed numerosity in memory for a 1 sec delay. They subsequently had to compare and match this memorized numerosity to a test stimulus. Using the sample period, we have previously shown that the monkeys treat empty sets as conveying a null numerical value; the detailed behavioral results have been reported in (Ramirez-Cardenas et al., 2016). This was evidenced by a ‘distance effect’ in the pattern of errors they made. Specifically, empty sets were erroneously matched to numerosity 1 more frequently than to numerosity 2. In the same study (Ramirez-Cardenas et al., 2016), we showed that neurons in the ventral intraparietal area (VIP) inside the intraparietal sulcus (IPS), as well as the dorsolateral prefrontal cortex (PFC) encoded numerosity, including empty sets, during the sample presentation period. In this paper, we therefore focus on the representation of numerosities 0 to 4 during the working memory period following sample presentation.

3.1. VIP and PFC single neurons represent empty sets during working memory

We recorded 861 single neurons from VIP, and 476 neurons in the PFC while the monkeys performed the task (Fig. 1C). In order to quantify the strength with which different stimulus factors are encoded by neuronal firing rates in time, we calculated the percentage of explained variance, specifically

shift. For each neuron the preferred numerosity of time-defined tuning curves was identified and the difference between consecutive preferred numerosities was calculated. Then these differences were cumulatively summed per neuron. The average in cumulative numerical shift over parietal and prefrontal neurons are shown in blue and red, respectively.

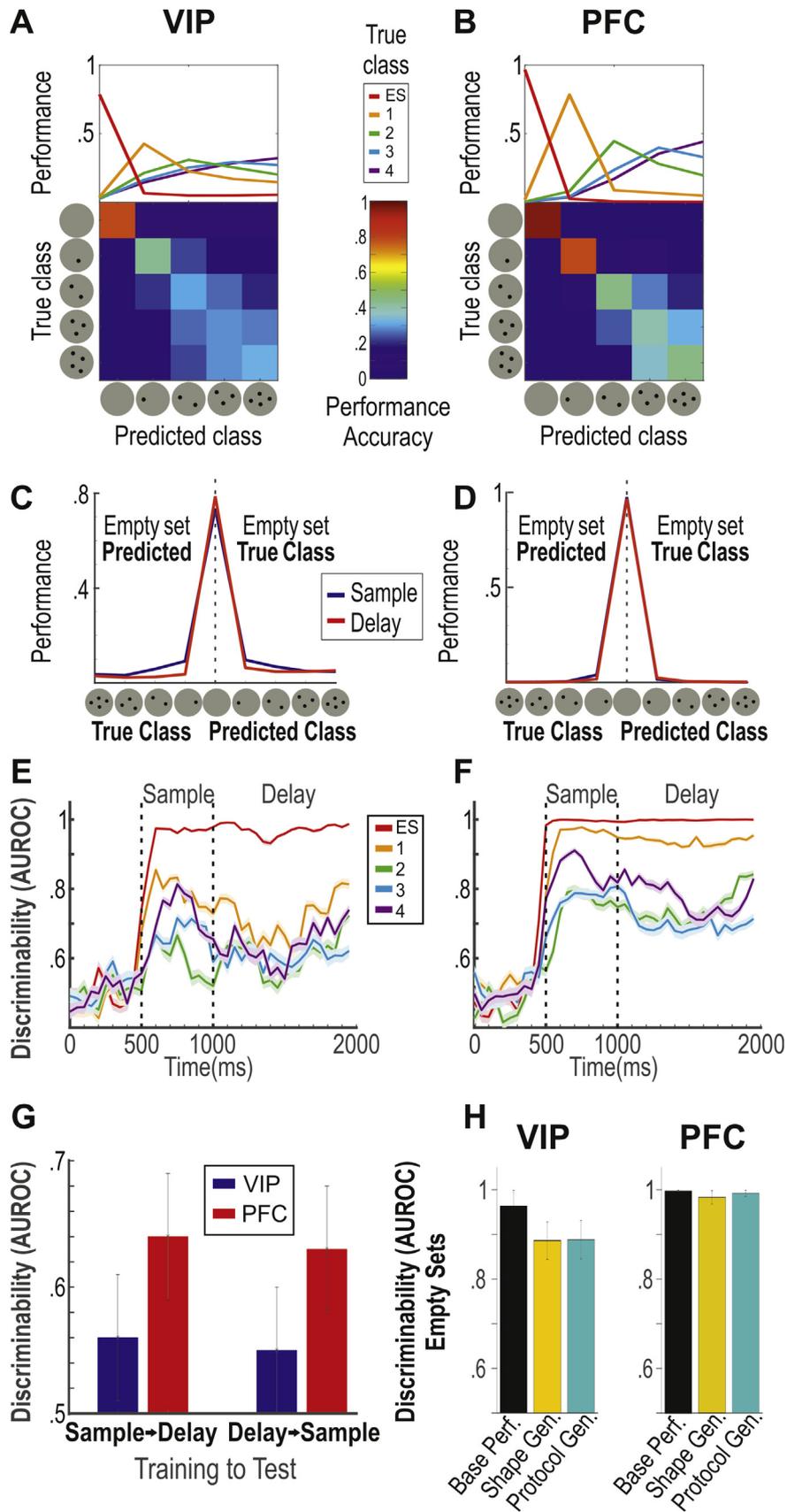


Fig. 5 – Decoding numerosities 0 to 4 using a statistical classifier. (A & B) General SVM Classifier accuracy performance during the delay period. Confusion matrices from the decoding performance of VIP and PFC classifiers in the memory period (delay). Numerosity was decoded from the spiking activity of parietal and prefrontal neuronal populations. The performance

omega squared (PEV, ω^2), from a sliding three-way-ANOVA (with main factors number, shape and protocol; 200 msec window, 20 msec step, 25 permutations) for each neuron in both cortical areas. Fig. 1D shows the mean ω^2 for factor sample numerosity across neurons in the whole population of parietal and prefrontal neurons. After the fixation period, number information is higher in PFC than in VIP.

Accordingly, in both cortical areas the activity of many neurons during the delay period was influenced by the numerosity that was shown in the previous sample period. Four example neurons that discriminated numerosity during the delay period are shown in Fig. 2. Fig. 2A shows a neuron from VIP that exhibited maximum discharge to empty sets during the memory delay; empty sets (“numerosity 0”) was the preferred numerosity. In contrast, the VIP cell in Fig. 2B responded least to empty sets. Similarly, empty sets caused the strongest (Fig. 2D) or weakest response (Fig. 2E) in PFC neurons.

The selectivity of all neurons was tested with a three-way ANOVA (with main factors number, shape and protocol), evaluated at $p < .01$. In the working memory phase (delay period), a proportion of VIP neurons (19.4%, 167/861) and PFC neurons (42.7%, 203/476) was significantly modulated by the numerosity previously presented as sample (Table 1). Fig. 2C,F depict the distribution of delay selectivity for the three main factors of single neurons in VIP and PFC, respectively.

Among the population of selective neurons in the delay period, we identified 75 VIP and 86 PFC neurons with a significant main effect for factor ‘number’ and no significantly modulated by any other main factor or factor interactions; these cells were called ‘exclusive number selective neurons’. To obtain population tuning functions, we normalized and averaged the tuning curves of exclusive selective neurons with the same preferred numerosity. In both VIP and PFC the population tuning curves for empty sets and countable numerosities exhibit a gradual decrease in the level of activity as the distance from preferred numerosity increases (‘distance-effect’) (Fig. 3A,C). This suggests that at the population level empty sets are correctly ordered in the context of other numerosities according to their null quantitative value.

We defined the preferred numerosity of each exclusive selective neuron as the stimulus that elicited the highest average firing rate. Fig. 3B,D shows the distribution of

Table 1 – Neuronal selectivity for the different task factors (3-factor ANOVA on delay-phase firing rates evaluated at $p \leq .01$).

ANOVA Factor	VIP (n = 861)	PFC (n = 476)
Number	19.4% (167)	42.7% (203)
Number only	8.7% (75)	18.1% (86)
Protocol	6.6% (57)	12.6% (60)
Shape	19.6% (169)	23.1% (110)
Number & Protocol	2% (17)	6.3% (30)
Number & Shape	3.4% (29)	11.6% (55)
Protocol & Shape	.8% (7)	3.6% (17)

preferred numerosities in VIP and PFC during the working memory epoch. Empty sets are the most frequently preferred stimulus in both VIP and PFC during the delay period (VIP 41/75, 54.7% and PFC 30/95, 34.9%). Compared to the sample phase, these proportions suggest an increase in the number of exclusive number-selective neurons preferring empty sets in the delay period, however this tendency does not reach statistical significance (increase of 14.7% in VIP, X^2 3.12, $p = .07$; and increase of 4% in PFC, X^2 .0131, $p = .9$, from sample to delay) [for data on the sample phase, please see Ramirez-Cardenas et al. (2016)]. Hereafter, neurons preferring empty sets will be referred to as ‘empty set neurons’ in this paper.

3.2. Behavior is correlated with the activity of PFC empty set neurons in the delay period

To explore the behavioral relevance of exclusive empty set neurons in either VIP or PFC for working memory, we analyzed delay activity in error trials and compared it to responses in correct trials. Particularly, we explored whether the firing rate of these neurons correlated with successful completion of the task. Only empty-set neurons with at least 3 error trials per compared stimulus category were considered in the analysis ($n = 13$ in PFC and $n = 10$ in VIP). If the responses of these neurons to empty sets (their preferred stimulus, i.e., eliciting maximal responses) were relevant for trial outcomes, lower firing rates would be expected in failed empty set trials. This was the case in prefrontal (Fig. 3G) but not parietal empty set neurons (Fig. 3E) (PFC: 13.96 ± 4.8 Hz versus 8.11 ± 2.65 Hz, for correct and error trials, $p < .01$, Wilcoxon signed-rank test,

curves for each true numerosity class are shown at the top of the confusion matrices. Each curve depicts the frequency with which the true class was labeled as other stimuli. (C & D) VIP and PFC classifier accuracy performance for empty sets in the sample and delay periods. In the right side of each plot the curves (blue for sample and red for delay) show how frequently true empty sets were labeled as different numerosities (sensitivity) by the classifier. In the left side of each plot the curves depict how frequently trials labeled as empty sets corresponded indeed to different numerosities (specificity). (E & F) Discriminability of different numerosities in the SVM classifier performance. Discriminability of each numerosity versus all others (AUROC, chance level .5) during the delay period in the SVM classifier performance. Discriminability was evaluated with AUROC values. (G) Transfer in the encoding of numerosity between the sample and delay epochs. The bar plot depicts numerosity discriminability (AUROC, chance level .5) when a SVM classifier is trained on the sample activity and tested on delay activity (left), and vice versa (right) in VIP (blue) and PFC (red). Error bars indicate the standard deviation over re-samples. (H) Generalization discriminability performance for empty sets in VIP and PFC classifiers. The bars depict the average discriminability of empty sets (AUROC, chance level .5) when training and testing were implemented in trials from different protocols (blue) or different background shapes (yellow). The black bars depict the base performance, when both training and testing were performed on a dataset including trials from all conditions. Error bars indicate the standard deviation over re-samples.

$n = 13$; VIP: 8.08 ± 2.04 Hz versus 5.9 ± 1.88 Hz, for correct and error trials, $p > .05$, Wilcoxon signed-rank test, $n = 10$). This result suggests that only the working memory activity of empty set neurons in PFC is relevant for the outcome of trials in which an empty set was presented as sample.

Next, we asked if the delay activity of empty-set neurons also correlated with the performance in countable numerosity trials. In correct trials, countable numerosities were encoded with low firing rates by empty set neurons. If this low activity was relevant for performance, higher firing rates to the non-preferred numerosities of empty set neurons might lead to errors. Therefore, we compared the firing rates of empty set neurons to their least preferred stimulus (a countable numerosity) in correct and error trials. During the delay period, PFC empty set neurons showed significantly lower firing rates in correct than in error trials involving their least preferred numerosity (Fig. 3G) (8.03 ± 1.65 Hz vs 9.41 ± 1.89 Hz, for correct and error trials, $p < .05$, $n = 48$, Wilcoxon signed-rank test). Again, this did not hold true for parietal empty set neurons (Fig. 3E) ($5.85 \pm .58$ Hz versus $6.06 \pm .58$ Hz, for correct and error trials, $p > .05$, $n = 81$, Wilcoxon signed-rank test). Both results combined indicate that only the activity of PFC empty set neurons affected the outcome of countable numerosity trials. Overall, the activity of PFC empty set neurons during the memory epoch is more robustly correlated with success or failure in completing the task.

Finally, to explore how the temporal profile of VIP and PFC number-selective neuronal activity contributes to the successful completion of the task we compared the dynamics of ω^2 (percentage of explained variance) for numerosity in correct and error trials. This measure indicates how much of the firing rate variability across trials is driven by the numerosity presented as sample in different moments of the trial. In this case, we included neurons with at least 2 error trials per numerosity category which are numerosity selective during either the sample or the delay period (regardless their tuning preference). Fig. 3F,H shows how ω^2 differs during correct and error trials in parietal and prefrontal neurons. In PFC (Fig. 3H), ω^2 is significantly lower in error trials during stimulus presentation (Sample $.046 \pm .001$ vs $.03 \pm .001$, $p = .041$; Delay $.03 \pm .003$ vs $.02 \pm .007$, $p = .056$, $n = 34$). In contrast, ω^2 does not differ significantly in VIP (Fig. 3F) during either the sample or the delay period (Sample $.033 \pm .007$ vs $.040 \pm .014$, $p = .98$; Delay $.019 \pm .003$ vs $.023 \pm .011$, $p = .74$, $n = 21$).

3.3. Empty sets are represented more categorically in working memory

To study the temporal dynamics of selectivity and tuning in the course of a whole trial we calculated firing rates and different analysis measures from sliding time windows (200 msec duration, 20 msec step). First, we identified the start and end times of numerosity selective responses in each neuron of the whole population using ω^2 (percentage of explained variance) as parameter. We then investigated how the tuning profile of empty set preferring responses changes in time.

Single neuron examples in Fig. 2 reveal that the tuning of empty-set preferring responses is more categorical late in the trial. Namely, during the delay period all stimuli containing dots (countable numerosities) elicit similar levels of activity,

which contrasts with the response to empty sets. This ‘categorical’ tuning can be depicted by a step-like function and entails a ‘something versus nothing’ representation of the stimulus range (Fig. 4A, top). In contrast, in a ‘continuous’ tuning profile the level of activity decreases as the distance from preferred numerosity increases (Fig. 4A, bottom). Single neuron examples suggested that this type of tuning is more prominent in the sample period than in the delay period. Following the approach used by (Engel, Chaisangmongkon, Freedman, & Wang, 2015), we fitted the tuning curve of each empty set response with a generalized linear model (GLM) that contained a linear combination of two regressor functions: a step-like function and a monotonically decreasing linear function (See Methods, Fig. 4B). β values correspond to the weight assigned to each regressor in the GLM and therefore reflect to what extent a particular tuning curve can be described as the corresponding category. From sample to delay, β values assigned to the step-function significantly increased while those assigned to the linear function decreased in both cortical areas (VIP: step function $.51 \pm .04$ vs $.6 \pm .02$, $p < .05$; linear function $.42 \pm .03$ vs $.3 \pm .02$, $p < .01$. PFC: step function $.47 \pm .04$ vs $.65 \pm .03$, $p < .001$; linear function $.48 \pm .04$ vs $.32 \pm .03$, $p < .01$, for sample and delay, respectively, Mann–Whitney U -test). Our results suggest that empty sets are represented more categorically in memory than during perceptual encoding.

3.4. A dynamic shift in population tuning toward empty sets

Neurons in the association cortices show flexibility and can change tuning preferences as a function of trial phases (Eiselt & Nieder, 2016). To quantify how general numerosity tuning changed throughout a trial, we derived time-defined tuning curves (sliding window of 200 msec width, 20 msec step) in neurons with exclusive numerosity selective responses in the delay period. Then, the tuning-curve cross-correlation for each neuron (Diester & Nieder, 2008) between subsequent pairs of tuning curves was calculated. This method quantifies the extent to which the shape of tuning curves changes from one time bin to another. High cross-correlation values (maximum 1) indicate similarity between the compared tuning functions, while lower values mark a change in neuronal tuning. Cross-correlation values are higher during the delay period in PFC than in VIP (PFC $.05 \pm .003$ $n = 179$ vs VIP $.04 \pm .005$ $n = 145$, mean CC baseline-corrected values over neurons \pm sem; $p < .05$, Mann–Whitney U -test) (See Methods, Fig. 4C). This finding suggests that during the memory period numerosity tuning is more stable in prefrontal than in parietal neurons.

Besides the shape of tuning curves, preferred stimulus is an important factor to consider when studying the tuning of neuronal responses. Therefore, we also tracked changes in the neurons’ number preference. We first identified, per delay selective neuron, the preferred numerosity of time-defined tuning functions and calculated the difference between consecutive pairs of preferred numerosities (numerical shift). Negative values indicate a preference shift towards smaller numerosities while positive values mark a preference shift towards larger numerosities. These differences between subsequent preferred numbers were cumulatively summed for

each neuron during the delay period. A decreasing cumulative shift over time indicates that numerical preference consistently changed in the direction of empty sets. Fig. 4D shows the mean cumulative numerical shift in the parietal (blue line) and prefrontal (red line) neuronal populations. We concluded that at the population level, stimulus preference progressively changes towards empty sets in VIP and PFC during the 1-sec period after the stimulus disappears, in the memory period. However, the dynamics of this change differs in VIP and PFC. The parietal cortex exhibits a progressive tendency toward empty sets along the whole delay period. Contrastingly, in PFC the negative shift evolves fast and is prominent in the first half of the delay period but stops afterwards. Overall, by the end of the delay period the change in preference towards empty sets is pronounced in the parietal cortex (Fig. 4D, $-.52$ VIP, $n = 145$; $-.40$ PFC, $n = 179$).

3.5. Decoding numerosity from working memory spiking activity

We used a decoding approach to assess how much information about numerosity is contained in VIP and PFC neuronal activity in the course of a trial. A support vector machine (SVM) classifier was trained to discriminate numerosity on the firing rates of either parietal or prefrontal neurons. For a fair comparison, we assembled pseudo-populations with similar numbers of neurons and balanced tuning preferences. We first trained the classifiers to discriminate each numerosity (5 classes, chance performance 20%). In the delay phase, classification accuracy was higher in PFC than in VIP throughout the delay period (VIP accuracy $42.7\% \pm 7.2\%$; PFC accuracy $60.7\% \pm 7.3\%$, mean \pm SD over resamples, training and testing in the same time bin) (Fig. 5A,B). In both cortical areas, the sensibility and specificity to identify empty sets increased from the sample to the delay period (Sensibility: VIP from 73.5% to 78.7%; Specificity: VIP from 77.3% to 87.2%). Performance confusion matrices showed that the tuning profile for empty sets became more categorical than graded (Fig. 5C,D) from sample to the delay, especially in VIP (Fig. 5E,F).

We further evaluated the ability of the classifier to discriminate each numerosity from all others using the area under the ROC-curve (AUROC, chance level .5) as measure (Fig. 5E,F). According to the ‘numerical size effect’, we would expect a graded decrease of discriminability with increasing numerosity. In comparison to the sample period, this pattern is less obvious during the delay period, predominantly in VIP. This reflects, again, a more categorical representation of the empty set in contrast to countable numerosities (‘something vs nothing’) at the population level.

To estimate to which extent the encoding of numerosity transfers between the sample and delay epochs, we trained the classifier on spiking activity elicited in one period and tested on the activity from other period (cross-training performance). When the classifiers were trained on sample activity and tested on delay activity numerosity discriminability (AUROC, chance level .5) in PFC was superior to VIP ($.56 \pm .05$ in VIP vs $.64 \pm .05$ in PFC, mean \pm SD over resamples, Fig. 5G). This result indicates that number encoding in the memory period can be better predicted from the previous activity during sample presentation at the prefrontal level. Vice versa, when

training was performed on delay activity and testing on sample activity, number discriminability was also better in PFC than in VIP ($.55 \pm .05$ in VIP vs $.63 \pm .05$ in PFC, mean \pm SD over resamples). Taken together, these findings suggest that the sensory and memory encoding of numerosity are more similar in PFC than in VIP, offering evidence that the prefrontal representation of number is more stable.

3.6. The representation of empty sets in VIP relies more on low level visual features than in PFC during the memory period

Finally, we investigated how invariant the representation of empty sets to low level and visual features in working memory is. For that purpose we performed generalization tests across conditions. For example, we trained a classifier on neural activity in standard trials and test it on activity from control trials, and vice versa. We also tested generalization across shape conditions (circle and square) (Fig. 5H). A decrease in performance when the training and test conditions differ evidences that stimulus discrimination relies on stimuli low level and image-like visual features. The discrimination performance of the prefrontal classifier was robustly preserved in generalization tests in the working memory period (from .998 to $.993 \pm .01$ in protocol and $.984 \pm .02$ in shape generalization tests for empty sets). In contrast to PFC, discriminability of empty sets in VIP decreased in shape generalization tests (accuracy dropped from $.97 \pm .04$ to $.89 \pm .04$, mean \pm SD) and protocol generalization tests (accuracy dropped from $.97 \pm .04$ to $.9 \pm .04$, mean \pm SD) (Fig. 5H). These results suggest that even during the working memory period, the parietal representation of empty sets relies more on low level visual features of the previously presented stimulus.

4. Discussion & conclusions

In the current study, we report that the representation for empty sets in working memory are also encoded by sustained activity in PFC and VIP, two areas considered at the core of the approximate number system (Nieder, 2016b). It is widely accepted that neurons showing selective sustained (or persistent) activity across temporal gaps keep task-relevant information ‘on line’ during working memory (Fuster & Alexander, 1971; Goldman-Rakic, 1987; Kubota & Niki, 1971), and that, working memory for numerical information relies on the interplay between prefrontal and parietal cortical regions (Jacob & Nieder, 2014). In the following, we compare the characteristics of delay cells in VIP and PFC and evaluate their putative behavioral relevance.

4.1. Sample versus delay activity to empty sets

The task design allows us to compare numerosity selectivity during the encoding (sample phase) and the memorization (delay phase) of the number of dots. In both VIP and PFC, a higher percentage of neurons preferred empty sets in the delay period with respect to sample presentation. This indicates a stronger encoding of empty sets in the memory period than in the encoding stage of the task.

During the sample or encoding stage of empty sets, VIP neurons were found to be more categorically tuned than PFC neurons, which showed a more gradual tuning function in agreement with the observed behavioral numerical distance effect (Ramirez-Cardenas et al., 2016). This difference between areas, however, was absent in the delay or working memory stage. In both areas, empty set neurons showed a more categorical tuning during the delay memory period than during perceptual encoding. It has been suggested that in working memory categorical representations are more economical and resistant to interference from distractors (Freeman, Rule, Adams Jr, & Ambady, 2010; Fukuda, Awh, & Vogel, 2010; Zhang & Luck, 2008). It is possible that a categorical representation of empty sets could be processed and subsequently manipulated more efficiently than a continuous representation. The change to a categorical encoding of empty sets in the delay period could be therefore advantageous.

4.2. Differential encoding of working memory for empty sets in VIP and PFC

Despite the presence of empty-set tuned neurons in both VIP and PFC, some interesting differences emerged between parietal and frontal lobes. All three parameters discussed below suggest sustained delay activity in PFC as being more directly relevant for the monkeys' judgment of 'nothing' (Merten & Nieder, 2012) and empty sets (Ramirez-Cardenas et al., 2016).

First, an analysis of delay activity in error trials relative to correct trials suggests that primarily numerosity-selective delay neurons in PFC are decision relevant. The assumption is that the monkeys' correct judgments rely on selective neurons that encode their respective preferred numerosity with maximum discharge. However, if such neurons respond with below maximum discharge rates, the monkeys would be prone to judgment errors. In VIP, no differential delay activity of empty-set neurons in correct or error trials was detected. The delay activity of VIP neurons tuned to empty sets was also indifferent during correct and error trials involving countable numerosities. This indicates that VIP neurons are not directly relevant for the working memory of numerosities. In contrast, empty-set delay tuned neurons in PFC showed significantly reduced responses during error trials compared to correct trials. Moreover, empty-set delay neurons exhibited significantly increased responses to countable numerosities during error trials. Both findings suggest that the delay responses of PFC empty-set tuned neurons are directly relevant for the monkeys performance.

Additional support for the prominent role of empty set neurons in PFC for behavior was found when we compared the stability of tuning from the sample to the delay period. Even though stimulus preference progressively changes towards empty sets during the delay period in both VIP and PFC, the change in preference towards empty sets is more pronounced in the parietal cortex by the end of the delay period. This indicates more stable tuning in PFC delay neurons.

Finally, the representation of empty sets by the population of prefrontal neurons during the delay period was more abstract. Using a classifier approach, we show that the parietal representation of empty sets relies more on low level visual features of the previously presented stimulus. When we

tested classifier performance generalization across shape (circle and square) and protocol (standard and control) conditions, VIP performance suffered significantly more than PFC performance. These results together suggest that PFC activity to empty sets and countable numerosities is more robust, abstract and behaviorally relevant than VIP activity.

4.3. Empty sets in a labeled-line code for number

We have previously reported that PFC and VIP neurons selective to countable numerosities showed peaked tuning functions to preferred numerosities, indicating a labeled-line code for the working memory of numerical information (Nieder et al., 2002; Nieder & Merten, 2007; Nieder & Miller, 2004). Neurons tuned to empty sets showed very selective tuning curves. On average, they exhibited a mild neuronal distance effect and responded slightly to the adjacent numerosity 1, but from numerosity 2 on the function was basically flat. This suggests that empty-set preferring delay neurons are better considered as detectors tuned to numerical value 0, rather than as summation units that show monotonically decreasing discharges as a function of number, as has been suggested for neurons selective to countable numerosities in area LIP (Roitman, Brannon, & Platt, 2007). Tuning to preferred numerosity has also been proposed by computational models of numerosity detection (Dehaene & Changeux, 1989; Verguts & Fias, 2004) albeit empty sets ("numerosity 0") was not part of the modeled number line.

Our results support the view that empty-set neurons are functionally similar to those selective to countable numerosities. This is supported by the finding of a distance effect in the tuning curves of the population empty-set neurons. Such a distance effect is characteristic for neurons tuned to countable numerosities (Nieder, 2017). Similarly, neurons tuned to countable numerosities responded to empty sets as value adjacent to one and thus included empty sets in their range of numerical responses.

4.4. Putative physiological mechanism to generate empty-set tuned working memory neurons

How can the brain produce sustained activity for empty sets that are characterized by the absence of any stimulus to be enumerated? While countable numerosities are represented spontaneously in human behavior (Anobile, Cicchini, & Burr, 2016; Burr & Ross, 2008; Cicchini, Anobile, & Burr, 2016) and by neurons in the monkey brain (Viswanathan & Nieder, 2013, 2015), representing empty sets requires explicit training about the meaning of quantity. We think that zero-like representations need to develop over time as the result of trial-and-error reinforcement learning to become behaviorally relevant. With behavioral feedback, reward prediction error signals arising from the dopamine system (Schultz, 2007) could modulate reward-dependent plasticity. Reinforcement learning could refine recurrent connections within associative cortical areas to support neuronal selectivity and sustained working memory coding (Law & Gold, 2009; Rombouts, Bohte, & Roelfsema, 2012). This has been modeled in a recent cortical circuit model from which category-selective neurons arose through reinforcement learning (Engel et al., 2015). In this model, weak but systematic

correlations between trial-to-trial fluctuations of the firing rates and the accompanying reward after appropriate behavioral choices cause neurons to gradually become category selective. Interestingly, initial tuning of the neurons is not required for successful learning. Even nonselective neurons can become category selective, as long as they carry neuronal fluctuations that correlate with behavioral choices. Such a mechanism might be enough to produce empty-set tuned neurons from originally untuned neurons when a subject learns the appropriate response to empty sets in order to receive a reward.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Author contributions

A.N. and A.R.C. designed research; A.R.C. performed research; A.R.C. analyzed data; A.N. provided analytical guidance; A.R.C. and A.N. wrote the paper.

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