

Basic mathematical rules are encoded by primate prefrontal cortex neurons

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Mathematics is based on highly abstract principles, or rules, of how to structure, process, and evaluate numerical information. If and how mathematical rules can be represented by single neurons, however, has remained elusive. We therefore recorded the activity of individual prefrontal cortex (PFC) neurons in rhesus monkeys required to switch flexibly between “greater than” and “less than” rules. The monkeys performed this task with different numerical quantities and generalized to set sizes that had not been presented previously, indicating that they had learned an abstract mathematical principle. The most prevalent activity recorded from randomly selected PFC neurons reflected the mathematical rules; purely sensory- and memory-related activity was almost absent. These data show that single PFC neurons have the capacity to represent flexible operations on most abstract numerical quantities. Our findings support PFC network models implementing specific “rule-coding” units that control the flow of information between segregated input, memory, and output layers. We speculate that these neuronal circuits in the monkey lateral PFC could readily have been adopted in the course of primate evolution for syntactic processing of numbers in formalized mathematical systems.

mathematics | monkey | number | single cell

Intelligent behavior requires strategic processing of numbers and abstract quantity information in accordance with internally maintained goals. In many everyday situations, our decisions on quantities are guided by mathematical rules applied to them, and mathematical principles also play a major role in our scientifically and technologically advanced culture (1–5). Nonhuman primates can perform basic arithmetic tasks on a par with college students, however, suggesting an evolutionarily primitive system for nonverbal mathematical thinking shared by man and monkey (6).

The semantic aspect of numerical quantity is represented by neurons in a frontoparietal cortical network, with the intraparietal sulcus (IPS) as the key node (7). Neurons in macaque IPS (8–10) and prefrontal cortex (PFC) (11–14) readily encode numerosities from visual displays and memorize them during delay periods. In humans, the detection of nonsymbolic numerosities and symbolic number information activates these sites in functional imaging studies (7, 15–17). Although the fundus of the IPS constitutes the first cortical site where quantities are extracted from sensory input, these quantities need to be processed further by integrating different sources of external and internal information to gain control over behavior. To that aim, numerical information from the IPS seems to be conveyed to the PFC, which operates on a higher hierarchy level (14).

We thus hypothesized that neurons in the PFC are ideally positioned to implement abstract response strategies required for basic mathematical operations. First, the PFC is particularly engaged during the processing of arithmetic operations requiring mathematical rules in humans (18–22), and damage to the PFC impairs reasoning with quantities (23–25). Second, PFC neurons can flexibly group information into behaviorally meaningful categories according to task demands (26–32). Consistent with these findings, lesions of human PFC cause deficits in rule-guided behavioral planning (33–36) and functional imaging studies show

strong PFC activation in tasks tapping the application of behavioral strategies (37, 38). Such processes are commonly summarized as executive control functions (39–41). Because mathematical principles operate on most abstract categories (e.g., quantities, numbers) rather than specific sensory stimuli, mathematical rules particularly require the highest degree of internal structuring. To investigate this, we recorded single-cell activity from the lateral PFC in macaques trained to compare set sizes (numerosities) and to switch flexibly between two abstract mathematical rules: a “greater than” rule and a “less than” rule.

Results

Behavioral Performance. We designed a simple rule-based numerical task and investigated if and how single neurons in the PFC represent basic mathematical rules. To that aim, we trained two rhesus monkeys to compare set sizes (numerosities) and to switch flexibly between two abstract mathematical rules. The greater than rule required the monkeys to release a lever if the first test display showed more dots than the sample display, whereas the less than rule required a lever release if the number of items in the test display was smaller compared with the first test display (Fig. 1). For each trial, the rule to apply (greater than vs. less than) was indicated by a cue that was present in the delay between sample and test stimuli. This enabled us to discern purely sensory-related signals in the sample period and purely memory-related signals in the delay 1 period from rule-related activity in the delay 2 phase. Because the animals additionally needed information about the numerosity of the test 1 display to prepare a motor response (whether to release or maintain the lever), preparatory motor-related activation could also be excluded from rule-related activation in the delay 2 phase. To dissociate the neural activity related to the physical properties of the cue from the rule that it signified, two distinct cues from different sensory modalities were used to indicate the same rule, whereas cues signifying different rules were from the same modality (Fig. 1 and *Methods*).

The monkeys learned the quantitative greater than and less than rules and were able to choose the smaller or greater set size relative to the sample numerosity independent of the absolute numerosity of the displays (Fig. 2). The monkeys ignored the particular visual appearance of the multiple-item dot displays and performed equally well in the standard (random dot sizes and dot density) and control (equal total dot area and dot density) conditions. Average correct performances in the standard and control conditions, respectively, were 92% and 91% for monkey B and 83% and 89% for monkey O, and this was significantly above chance level ($P < 0.001$, binomial test). Moreover, the animals' performance was comparable for the two rule cue modalities (red/blue vs. water/no-

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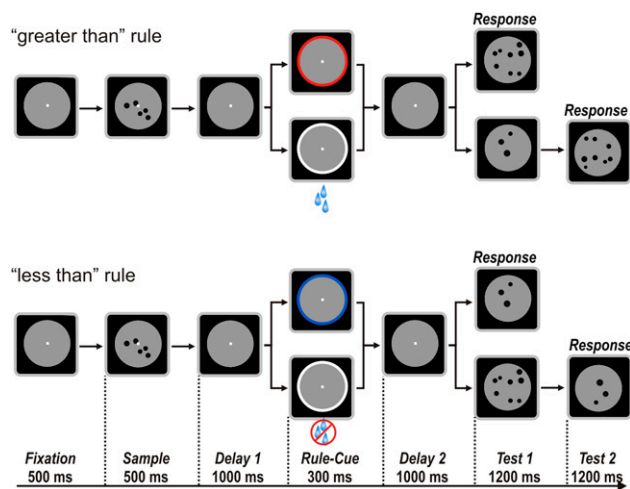


Fig. 1. Behavioral protocol. Monkeys grasped a lever and maintained central fixation. A sample numerosity was followed by a brief working memory delay (delay 1). Next, a cue indicated either the greater than or less than rule ($P = 0.5$ for each rule). Each rule was signified by two different sensory cues (red and water for the greater than rule, blue or no-water for the less than rule; first bifurcating arrows), followed by a rule delay (delay 2) requiring the monkeys to assess the rule at hand for the subsequent choice. For each rule, two trial types are illustrated (second bifurcating arrows). (*Upper*) For the greater than rule, the monkeys released the lever if more dots were shown in the first test display than in the sample display; otherwise, they held the lever until the appearance of a second test display that always required a response. (*Lower*) For the less than rule, the lever had to be released if the numerosity in the first test display was smaller than that in the sample display. Thus, only test 1 required a decision; test 2 was used so that a behavioral response was required on each trial, ensuring that the monkeys were paying attention during all trials.

water) (Fig. 2 *A* and *B*). Most importantly, the monkeys immediately generalized the greater than and less than rules to numerosities that had not been presented previously (*Methods*). Fig. 2 *C* and *D* shows the monkeys' high performance to the first session with sample numerosities that had not been presented previously, and this performance remained stable over several sessions (Fig. 2 *E* and *F*). This indicates that they understood this basic mathematical principle irrespective of the absolute numerical value of the sample displays.

Single PFC Neurons Encode Mathematical Rules. We recorded the activity of 484 randomly selected single neurons in the lateral PFC on both banks of the principal sulcus (Fig. 3 *A* and *B*), whereas the two monkeys flexibly switched between the greater than and less than rules. Neuronal selectivity was determined in the four task periods: sample, delay 1, cue, and delay 2. Table 1 shows that only a few neurons were selectively tuned to sample numerosity in the sample and delay 1 periods (two-way ANOVA, with factors [sample numerosity] \times [numerosity protocol]; $P < 0.01$; only a significant numerosity main effect, with no other main effects or interactions present). During the rule cue period, most of the selective neurons (Table 1) were tuned to the modality of the rule cue (four-way ANOVA, with factors [sample numerosity] \times [numerosity protocol] \times [cue modality] \times [rule]; $P < 0.01$).

In the delay 2 period, however, the first phase in which the monkeys had been informed about the mathematical rule to apply, but before they could know how to respond to the test display, rule selectivity emerged with duration of the delay 2 period. During the first half of the delay 2 period, many neurons encoded both the cued rule and the cue modality (resulting in a high proportion of cells exhibiting interaction between main factors) (Table 1). In the second half of the delay 2 phase,

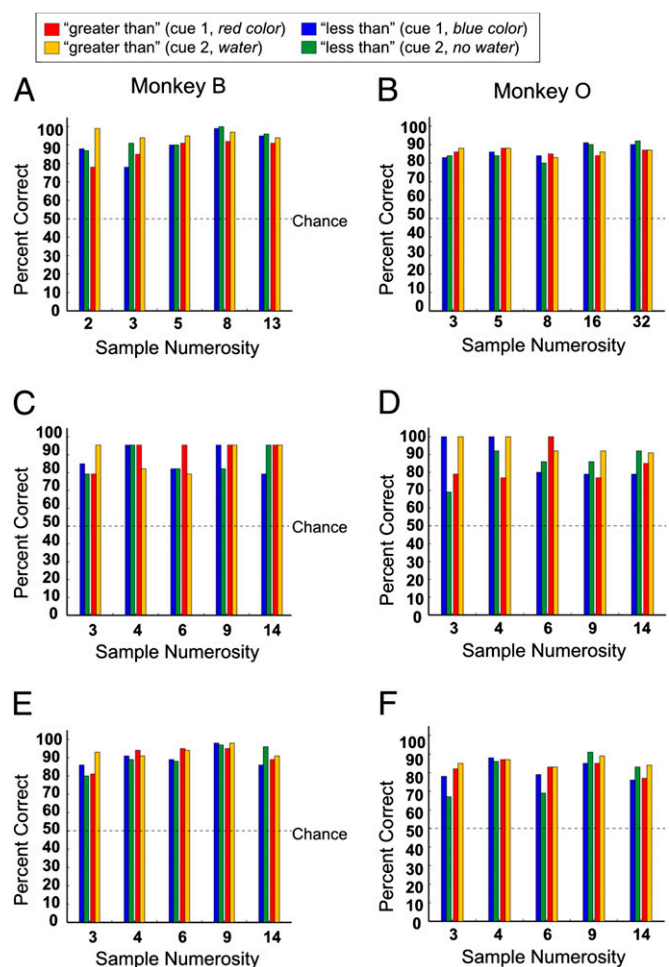


Fig. 2. Behavioral performance. Columns show percent correct responses of the two monkeys for the greater than and less than tasks. (*A* and *B*) Performance of monkey B and monkey O during electrophysiological recordings (standard and control protocols pooled). (*C–F*) Generalization task. Task performance of monkey B (*C*) and monkey O (*D*) in the first session with sample numerosities not previously presented. (*C*) Each data point (i.e., bar) represents a minimum of 4 trials and a maximum of 9 trials for monkey B. (*D*) For monkey O, the minimum and maximum trial counts in this first generalization session were 10 and 16 trials, respectively. Generalization performance of both monkeys to the previously unpresented sample numerosities pooled for seven (*E*) and six (*F*) sessions. Both monkeys performed significantly above chance level (50%) for all sample numerosities, cues, and rules.

however, the highest proportion of neurons [90/484 (19%)] showed activity that varied significantly and exclusively with the cued rule. Therefore, we confined all further analyses to the second half of the delay 2 period. Rule selectivity was independent of the sample numerosity, the stimulus protocol, or the sensory rule cues (four-way ANOVA; only significant rule was a main effect, with no other main effects or interactions present). Of the 90 purely rule-selective neurons in the second half of delay 2, greater than (50 cells) and less than (40 cells) neurons were about equally frequent. All displays and analysis in Figs. 3–6 are based on purely rule-selective neurons. Only a few neurons showed a main effect for numerosity, stimulus protocol, or cue modality in the second half of the delay 2 phase (Table 1).

Two example pure rule-selective neurons are shown in Fig. 3 *C–F*. The neuron in Fig. 3 *C* and *D* discharged preferentially to the greater than rule and generalized over the sensory rule cues, whereas the cell in Fig. 3 *E* and *F* showed inverse selectivity and discharged strongest to the less than condition. Fig. 4 shows the

Table 1. Neural selectivity in different task periods (484 neurons)

Percentage of cells selective for	Sample*	Delay 1*	Cue†	Delay 2†(first half)	Delay 2†(second half)
Only sample numerosity	3.5	4.3	0.4	1.3	3.7
Only numerosity protocol	0.6	0.8	0.0	0.6	1.5
Only cue modality	—	—	10.9	7.8	4.1
Only rule	—	—	2.0	7.4	18.6
Any interaction between main factors	1.0	0	1.6	13.8	6.4

*Two-factor ANOVA.

†Four-factor ANOVA.

detailed responses of a third pure rule-selective neuron during the second half of the delay 2 period; this neuron always preferred the greater than rule, irrespective of the displayed sample numerosities. Note that all three neurons in Figs. 3 and 4 developed rule selectivity several hundred milliseconds after cue offset. This latency may reflect the time the monkeys needed to deduce the appropriate rule from the sensory cues. Alternatively, neurons in the PFC may acquire rule representation only immediately before the rule information is needed, thus reflecting certainty that the rule will need to be applied soon.

To characterize the quality of rule selectivity in the PFC in more detail, we determined quantitatively whether neurons responded more strongly to the greater than or less than rule. We used a receiver operating characteristic (ROC) analysis (42) to determine whether and how activity of the ANOVA pure rule-selective neurons differed in the two rule conditions. This ROC analysis was performed over the same 500-ms time window used for the ANOVA during the second half the delay 2 period. The ROC values indicate the degree of separation between two distributions of discharge rates, independent of the cell's overall activity and dynamic range. By convention, we used the responses to the less than rule as the reference distribution; thus, ROC values >0.5 characterized cells that responded more strongly to the greater than rule. Except for four neurons (two for the greater than rule and two for the less than rule), all ROC values were significantly different from 0.5 ($P < 0.05$, permutation test; $n = 86$). The bimodally distributed data (Fig. 5A) indicate that approximately half of the selective neurons preferred the greater than rule, whereas the other half preferred the less than rule (binomial test, $P > 0.05$). ROC values for the greater than rule (0.62) and less than rule (0.38) were not different ($P > 0.05$, Mann-Whitney U test). This confirmed that both rules were represented about equally by the neuronal discharges.

We next characterized how neurons represented quantitative rules across time during the delay 2 period. A sliding-window ROC analysis applied to consecutive overlapping time windows of 100 ms (advanced in steps of 20 ms) revealed that different neurons encoded quantitative rules during different overlapping time segments (Fig. 5B). With time after rule cue offset, an increasing number of cells ($n = 78$, latency could not be determined in eight neurons) became selectively tuned to the rules (latency determined as the first bin significantly different from 0.5 occurring 240 ms after rule cue offset; permutation test, $P < 0.05$). Across the population of neurons, signals representing rules developed progressively after the rule cue and increased in quality (i.e., average ROC values increased) toward the beginning of the test period (Fig. 5C and D).

PFC Activity Predicts Successful Rule Application. If rule-selective neurons constitute a neuronal correlate for the monkeys' ability to choose greater than/less than rules, the neurons' selectivity should be weaker whenever the monkeys failed to derive the correct rule, and thus chose wrongly. To address this issue, we compared the neuronal responses of individual rule-selective neurons when the monkeys made correct choices with trials with behavioral errors. Average discharge rates were significantly

decreased by 9.4% when the monkeys made rule errors relative to correct choices ($P < 0.01$, Wilcoxon signed rank test, two-tailed; $n = 90$). Fig. 6A shows the time course of a representative neuron's responses in correct and error trials. The discharge to the preferred greater than rule is largely reduced toward the end of the delay 2 period. For the population of selective neurons, median ROC values were decreased from 0.614 in correct trials to 0.594 in error trials ($P < 0.01$, Wilcoxon signed rank test, two-tailed; $n = 86$). As a consequence, the bimodal distribution of ROC values deteriorated in error trials (Fig. 6B). These findings argue that single PFC neurons represent basic mathematical rules and guide greater than/less than decisions.

Discussion

Our results demonstrate that PFC neurons can flexibly represent highly abstract mathematical rules. We found that this is accomplished by quite specific rule-selective neurons at the expense of lower level sensory and working memory representations. These findings elucidate the neurobiological mechanisms of operations on numbers and pave the way for a better understanding of the processing of basic mathematical rules in the primate brain.

Behavior. To use greater than/less than rules, the monkeys were required to understand relations between numerosities and how to apply them successfully in a goal-directed manner. We presented the animals with a large number of unique trials per session (160 in total) that were repeated three times at most during a single session (*Methods*). Thus, it was impossible for the animals to solve the task by quickly learning, on each day, a set of 160 associations. Instead, the monkeys had to rely on principles of relations between quantities that hold irrespective of the numerical values of the sample and test displays and the rule cue modalities (Fig. 2A and B). Thus, the animals immediately generalized the greater than and less than rules to sample and test numerosities that had not been presented previously (Fig. 2C-F).

Selectivity to Basic Mathematical Rules in PFC. Damage to the PFC typically causes deficits in switching between different abstract rules (33-36), and PFC neurons in monkeys have been shown to encode abstract rules in a "match/nonmatch" task (28) as well as during changing response strategies (29, 31). Here, we report that almost 20% of randomly selected PFC neurons encode basic mathematical rules. Among the four task components analyzed (sample numerosity, numerosity protocol, rule cue modality, and rule), the most prevalent neuronal activity reflected the greater than and less than rules, which were represented about equally by single neurons. Rule-selective activity was not encoded instantaneously but needed time to develop. We suspect this to be a reflection of a time-consuming neuronal process that derives from the cue of the corresponding rule semantics. Alternatively, it may represent a demanding retrieval process of rule information from other brain areas.

The quality of rule selectivity for mathematical rules in our study (median ROC = 0.614) was slightly higher than that found for match/nonmatch rules (0.57) by Wallis and Miller (43) and

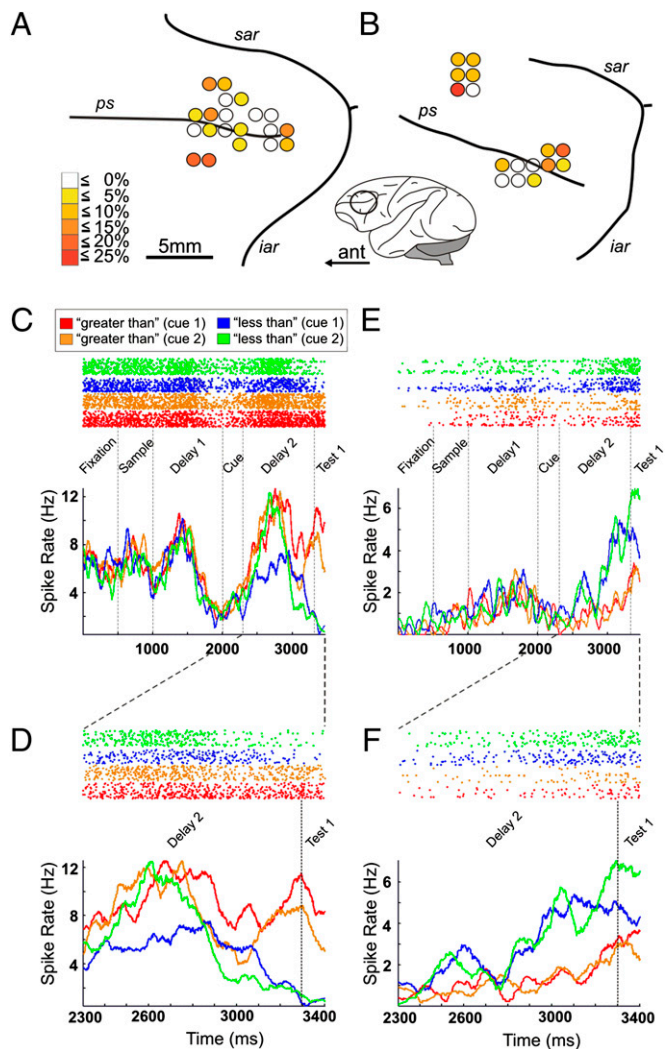


Fig. 3. Single-cell recordings. Location of recording sites in monkey B (A) and monkey O (B). The percentage of proportion-selective units found at each recording site is color-coded. (B, *Inset*) Lateral view of a rhesus monkey brain. The circle indicates the location of the recording chamber. ant, anterior; iar, inferior arcuate sulcus; ps, principal sulcus; sar, superior arcuate sulcus. (C and D) Typical rule-selective example neuron 1 selective for the greater than rule toward the end of the delay 2 (second half) phase. Responses across the entire trial (C) and magnified during the delay 2 period (D) are shown. (*Upper*) Neuronal responses are plotted as dot-raster histograms (each dot represents an action potential, spike trains are sorted and color-coded according to the rules and rule cues). (*Lower*) Spike density functions (activity averaged over all trials and smoothed by a 150-ms Gaussian kernel). Rule selectivity was regardless of which cue signified the rule. (E and F) Example neuron 2 selective for the less than rule (same layout as in C and D). Only responses to correct trials are shown.

comparable to that found for neurons reflecting repeat-stay and change-shift strategies (0.615) by Genovesio et al. (31). (Note that different durations of analysis windows and different numbers of trials per cell in the three studies limit the comparability of ROC values.)

An analysis of trials in which the monkeys made judgment errors further emphasizes the significance of rule-related activity for correct choices. If the animals made wrong decisions, the spike rates and ROC values in the delay 2 period were significantly reduced. In other words, whenever the rule detectors did not properly encode “their” rule by maximum discharges, the animals had a higher tendency to fail.

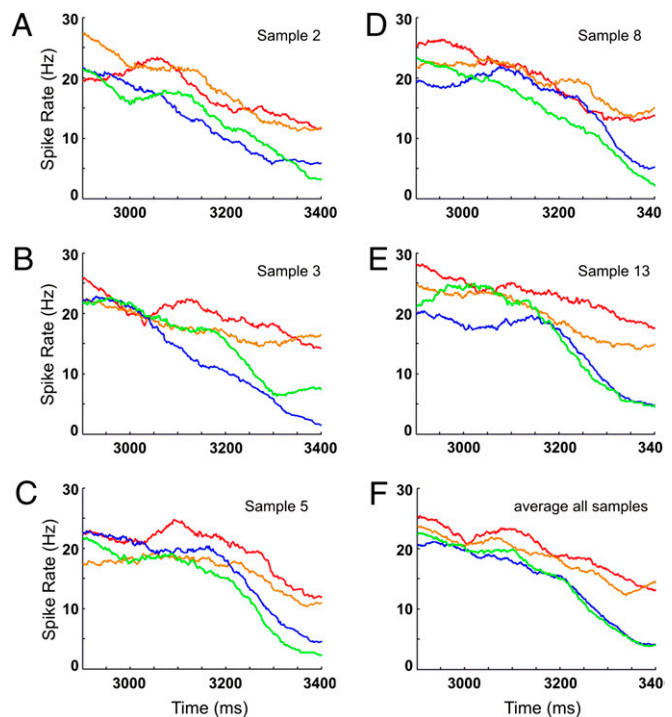


Fig. 4. Detailed responses of a rule-selective neuron. Spike-density histograms of a third example neuron in the delay 2 (second half) period are shown. The neuron showed higher activity to the greater than rule, irrespective of whether sample numerosity 2 (A), 3, (B), 5 (C), 8 (D), or 13 (E) was shown. (F) Average discharges across all sample numerosities. Only responses to correct trials are shown.

Predominance of Rule Selectivity Over Sensory- and Memory-Related Activity.

The task-switching protocol we used enabled us to discern sensory-related (sample) and working memory-related (delay 1) activity from rule-selective activity (delay 2). We found that very few neurons were tuned to the numerical value of the sample display in the demanding task-switching task. Such activity was virtually absent even in the memory delay periods. Because carrying information across delays is thought to reflect working memory, a hallmark function of PFC (40), this finding is particularly surprising and in striking contrast to those of many studies using delayed response tasks (44) as well as our previous recordings from the PFC. There, about one-third of randomly selected PFC neurons were significantly tuned to numerosity during a delayed matching task (11–14). Neurophysiological differences between individuals are unlikely to account for this discrepancy, because one of the monkeys participating in the current study (monkey B) also exhibited the typical high proportion of numerosity-selective PFC neurons in a previous delayed match to numerosity study (14). Most likely, thus, these coding differences are related to the functional properties of PFC neurons.

As long as task demands are low, it seems that the highly adaptable cells in the PFC (45) can afford to code low-level sensory stimulus features and intermediate-level working memory signals. If a task demands an increase, however, a division of coding labor is required and the PFC is released from lower level representations that limit its cognitive resources (see the article by Gold and Shadlen (46) for similar findings in the frontal eye field). To reveal its sophisticated coding capacities, we hypothesize that the PFC needs to be “challenged” with complicated task components. This would (also) be consistent with the general finding that damage to the lateral PFC spares low-level functioning, although causing impairments of intricate high-level mental processes (23–25, 33–36).

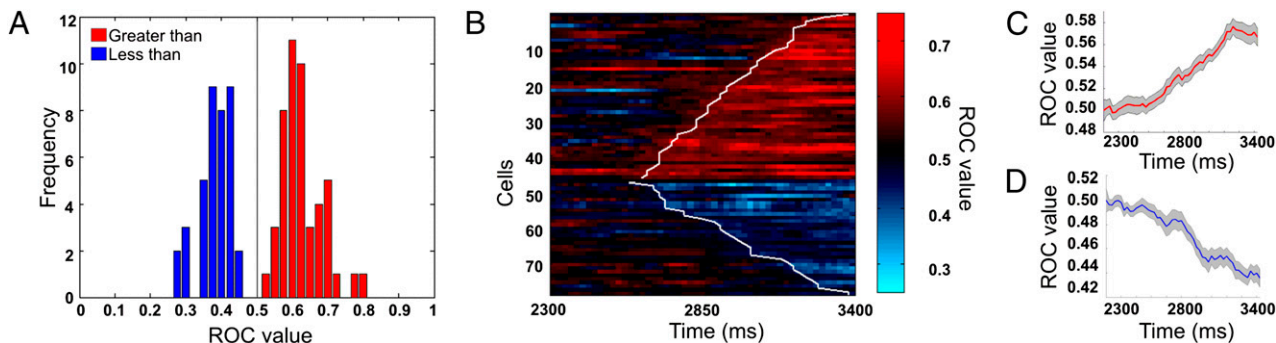


Fig. 5. PFC neurons encode the greater than and less than rules. (A) Frequency histogram of ROC values of neurons encoding the abstract quantitative rules during correct trials in the delay 2 (second half) period. (B) Temporal evolution of rule-selective signals in the second half of the delay 2 period. Each row in the color map represents rule-selective coding for an individual neuron, with neurons preferring greater than (red) and less than (blue) sorted in opposite order according to the first time point where the ROC value significantly differed from 0.5. White curves depict the neurons' latency for rule selectivity. Time 0 ms is the onset of the delay 2 period. Average ROC values are shown as a function of time during delay 2 (second half) for all neurons preferring the greater than (C) or less than (D) rule.

Our finding that PFC neurons specifically represent the rules at hand is in good agreement with a PFC neural network model proposed by Dehaene and Changeux (47) for the classic neuropsychological Wisconsin Card Sorting Test (WCST). In the WCST, a deck of cards needs to be sorted according to different changing rules (color, form, or number of card signs). According to this model, separate rule-coding clusters represent the rules of the game. Each rule-coding cluster codes for a particular sorting rule and gates a corresponding subset of internal memory (for input) clusters and intention (for output) clusters. Such specific rule-coding clusters in the network are mirrored by our finding of a physiological predominance of rule-selective neurons that specifically respond to the larger than and less than rules.

The current data therefore beg two questions: (i) Where is the information about number categories originally encoded during sensory presentation, and (ii) where is it maintained online in working memory? An ideal candidate structure for extracting and storing numerosity in working memory is the posterior parietal cortex (7). Neurons in the IPS have been shown to encode numerosity, both explicitly (8, 9) and implicitly (10), and also to maintain numerical information online during a delay period (8, 9). In addition, or alternatively, neurons in other parts of the frontal lobe, such as the anterior cingulate cortex (29), premotor cortex (43), or even parietal (48) or subcortical areas (49), could also be engaged. Recordings from different cortical and subcortical regions could help to elucidate the complete network of brain regions necessary for solving basic mathematical tasks.

Methods

Behavioral Protocol. Monkeys learned to perform numerical greater than and less than comparisons flexibly based on varying rules. In each trial (Fig. 1), a sample stimulus cued the animals for the reference numerosity they had to remember for a brief time interval. The first memory interval (delay 1) was followed by a rule cue that instructed the monkeys to select a numerosity either larger (greater than rule) or smaller (less than rule) than the sample numerosity in the subsequent test phase to receive a liquid reward.

Because both sample and test numerosities varied systematically, the monkeys could only solve the task by assessing the numerosity of the test display relative to the five possible numerosities of the sample display together with the appropriate rule in any single trial. To test a broad range of numerosities, monkey B was presented with sample numerosities 2 (smaller test numerosity = 1, larger test numerosity = 3), 3 (2: 5), 5 (3: 8), 8 (5: 13), and 13 (8: 19). Monkey O was tested with sample numerosities 3 (1: 5), 5 (3: 8), 8 (5: 16), 16 (8: 32), and 32 (16: 64). For any sample numerosity, test numerosities were either larger or smaller with equal probability ($P = 0.5$). Because the monkeys' numerosity discrimination performance obeys the Weber–Fechner law (12), numerosities larger than a sample numerosity need to be numerically more distant than numerosities smaller than the sample numerosity to reach equal discriminability. Based on this design, any numerosity (except the smallest and largest used) served as sample and test numerosities, thus precluding the animals from learning systematic relations between numerosities.

To prevent the animals from exploiting low-level visual cues (e.g., dot density, total dot area), standard (dot size and position randomized) and control (equal total area and average density of all dots within a trial) numerosity protocols were presented in a randomized fashion. To dissociate the rule-related cellular responses from responses to the sensory features of the rule cue, each rule was signified in two different sensory modalities: A red circle and a drop of water delivered with a white circle signified the rule greater than, whereas a blue circle and no water delivered with a white circle cued the rule less than. To test if monkeys could generalize the mathematical principle to numerosities that had not been presented previously, both monkeys

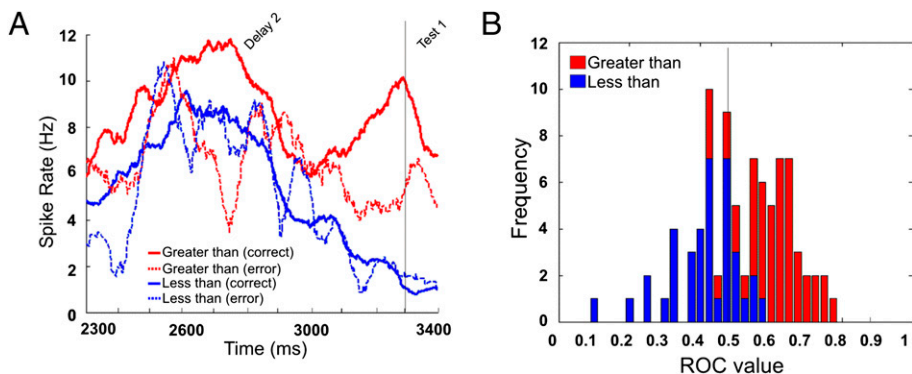


Fig. 6. Rule selectivity during error trials. (A) Discharges of a representative neuron during a monkey's correct vs. erroneous choices. (B) Frequency histogram of ROC values during the second half of the delay 2 phase of neurons encoding the two abstract rules during error trials.

additionally performed the task with sample numerosities 3 (smaller test numerosities: 1 and 2; larger test numerosities: 4 and 5), 4 (1, 2: 6, 7), 6 (2, 4: 9, 12), 9 (3, 6: 13, 16), and 14 (7, 10: 18, 20). Thus, in any given session, the animals were confronted with 160 unique trials [5 sample numerosities four times \times 2 stimulus protocol types (standard/control) \times 2 rules \times 2 cue modalities], which were repeated up to three times per session. After each session, the displays were generated anew using Matlab (Mathworks).

Trials were randomized and balanced across all relevant features (e.g., greater than and less than rules, rule cue modality, sample numerosities). Monkeys had to keep their gaze within 1.75° of the fixation point from the fixation interval up to the onset of the first test stimulus (monitored with an infrared eye-tracking system; ISCAN, Burlington, MA).

Neuronal Recording. Recordings were made from the left PFC of two rhesus monkeys (*Macaca mulatta*) in accordance with the guidelines for animal experimentation approved by the Regierungspräsidium Tübingen, Germany. Arrays of eight tungsten microelectrodes (1-M Ω impedance) were inserted using a grid with 1-mm spacing. Recordings were localized using stereotaxic reconstructions from individual magnetic resonance images. Neurons were selected at random; no attempt was made to search for any task-related activity. Signal amplification, filtering, digitizing of spike waveforms, and spike sorting were accomplished using the Plexon system (Dallas, TX). Separation of all single-unit waveforms was performed off-line.

Data Analysis. Activity in the different task periods was separately analyzed. For the sample period, discharge rates were measured in a 500-ms window starting 100 ms after sample onset. Purely working memory-related activity in the delay 1 period was assessed in an 800-ms window starting 200 ms after sample offset. Responses to cue modality were assessed in a 300-ms window

beginning 100 ms after rule cue onset. Rule-selective activity in the delay 2 period was analyzed in two consecutive 500-ms windows starting 100 ms (first half) and 600 ms (second half), respectively, after delay 2 onset. A two-way ANOVA with the main factors of sample numerosity (five numerosities) and numerosity protocol (standard and control protocols) was evaluated at $P < 0.01$ in the sample and delay 1 periods. From the cue period on, a four-way ANOVA with the main factors of sample numerosity (five numerosities), numerosity protocol (standard and control protocols), rule cue modality (color vs. water), and rule (greater than vs. less than) was evaluated at $P < 0.01$.

In addition, we compared spike counts in the two rule conditions using a ROC analysis (42) of neurons classified as purely rule-selective based on the ANOVA. This ROC analysis was performed over the same 500-ms time window used for the ANOVA during the second half of the delay 2 period. We also characterized the temporal evolution of individual neurons' rule selectivity by computing a sliding ROC analysis in 100-ms windows moved in 20-ms steps across a trial's delay 2 period and the first 100 ms of the test 1 period. Discharges in error trials were compared with those in correct trials using raw spike counts from the same 500-ms window used for the ANOVA as well as the ROC values. To derive error-ROC values, activity of a greater than ("smaller than") neuron for trials in which the monkey correctly chose the larger (smaller) numerosity was compared with the same neuron's activity when the animal erroneously chose the smaller (larger) numerosity.

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