Rule Activity Related to Spatial and Numerical Magnitudes: Comparison of Prefrontal, Premotor, and Cingulate Motor Cortices

Anne-Kathrin Eiselt and Andreas Nieder

Abstract

■ In everyday situations, quantitative rules, such as "greater than/less than," need to be applied to a multitude of magnitude comparisons, be they sensory, spatial, temporal, or numerical. We have previously shown that rules applied to different magnitudes are encoded in the lateral PFC. To investigate if and how other frontal lobe areas also contribute to the encoding of quantitative rules applied to multiple magnitudes, we trained monkeys to switch between "greater than/less than" rules applied to either line lengths (spatial magnitudes) or dot numerosities (discrete numerical magnitudes). We recorded single-cell activity from the dorsal premotor cortex (dPMC) and cingulate motor cortex (CMA) and compared it with PFC activity. We found the largest proportion of quantitative rule-selective cells in PFC (24% of randomly selected cells), whereas neurons in dPMC and CMA rarely encoded the rule (6% of the cells). In addition, rule selectivity of individual cells was highest in PFC neurons compared with dPMC and CMA neurons. Rule-selective neurons that simultaneously represented the "greater than/less than" rules applied to line lengths and numerosities ("rule generalists") were exclusively present in PFC. In dPMC and CMA, however, neurons primarily encoded rules applied to only one of the two magnitude types ("rule specialists"). Our data suggest a special involvement of PFC in representing quantitative rules at an abstract level, both in terms of the proportion of neurons engaged and the coding capacities. ■

INTRODUCTION

Relating objects as larger or smaller, or more or less than other objects based on the property "magnitude" is a comparison we use in everyday life to arrive at informed decisions. We process relations between magnitudes such as size or number flexibly by applying "greater than/less than" quantitative rules. For instance, when hungry, we follow a "greater than" rule applied to an innumerable magnitude when choosing the size of a slice of pizza. We also use a "greater than" strategy when we are faced with countable magnitudes, for example when negotiating the number of dollar bills of our salary. But how are such quantitative rules neuronally encoded when applied to different abstract magnitude types?

The PFC is a key area in representing cognitive components required for abstract goal-oriented behavior. PFC neurons encode multiple categories (Pan & Sakagami, 2012; Cromer, Roy, & Miller, 2010; Roy, Riesenhuber, Poggio, & Miller, 2010) and abstract numerical information (Nieder, 2013; Viswanathan & Nieder, 2013; Genovesio, Tsujimoto, & Wise, 2011; Tudusciuc & Nieder, 2007, 2009; Nieder, Freedman, & Miller, 2002) in combination with abstract rules (Kamigaki, Fukushima, Tamura, & Miyashita, 2012; Vallentin, Bongard, & Nieder, 2012; Bongard & Nieder, 2010; Stoet & Snyder, 2009; Genovesio, Brasted, Mitz, & Wise, 2005; Wallis, Anderson, & Miller, 2001; White & Wise, 1999). PFC is therefore ideally positioned to represent rules applied to multiple magnitude types.

In a recent study, we recorded from PFC neurons while monkeys switched between "greater than/less than" rules applied to spatial and numerical magnitudes. We found that PFC neurons not only encoded quantitative rules as independent principles (i.e., rules only applied to a single magnitude type), but more neurons than expected by chance also responded to the overarching concept "magnitude rules," signaling quantitative rules irrespective of magnitude types (Eiselt & Nieder, 2013). Thus, besides rule-specialized neurons ("specialists") also rule-generalizing cells ("generalists") were involved in selecting magnitudes based on rules.

However, PFC does not operate in isolation, but rather is part of a wider frontal lobe network. The outputs of PFC are sent to motor-related areas (Miyachi et al., 2005; Bates & Goldman-Rakic, 1993; Barbas & Pandya, 1987) and different studies suggested that such premotor areas convey even stronger abstract rule activity (Vallentin et al., 2012; Muhammad, Wallis, & Miller, 2006; Wallis & Miller, 2003). For example, Muhammad et al. (2006) and Wallis and Miller (2003) found stronger rule-related activity in a same/different task and report that these signals appeared earlier in premotor cortex (PMC) compared with PFC. This suggests a more pronounced role of the PMC in encoding abstract rules.

University of Tübingen

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Further evidence for the important role of PMC in rule following comes from Vallentin et al. (2012). They report a similar fraction of neurons in PFC and dorsal PMC (dPMC) representing numerical "greater than/less than" rules and that this rule-related activity was also stronger in dPMC neurons. Besides PMC, also other frontal areas, like the ACC or cingulate motor areas (CMAs), are thought to be critically engaged in rule-guided behavior (Womelsdorf, Johnston, Vinck, & Everling, 2010; Buckley et al., 2009; Johnston, Levin, Koval, & Everling, 2007), action selection (Paus, 2001; Shima & Tanji, 1998), and abstract decision-making (Merten & Nieder, 2013) and have been recently found to also represent numerical quantitative rules, although to a much lesser extent (Vallentin et al., 2012). In the current study, we thus compared the roles of three different brain areas in the frontal lobe, the PFC, dPMC, and CMA, in representing multiple abstract rules.

METHODS

Subjects

We recorded neural activity from two macaque monkeys (*Macaca mulatta*, Monkey O: 8 kg, male; Monkey E: 4 kg, male) that were cared for in accordance with the guidelines for animal experimentation approved by the Regierungspraesidium Tübingen, Germany. Both monkeys were trained first on the numerosity comparison followed by the line length comparison. Recordings from PFC of Monkeys O and E are described in Eiselt and Nieder (2013).

Behavioral Task and Stimuli

We trained two monkeys to perform a "greater than" and "less than" comparison and to flexibly switch between two different magnitude types (or categories): the length of a line (spatial magnitude) and the number of dots in a set (numerosity, discrete magnitude), which both were presented in three different sample values with corresponding match and nonmatch values (for details, see Eiselt & Nieder, 2013). To initiate a trial, the monkeys had to grasp a response bar and fixate a central fixation target (Figure 1A, B). Eye movements were monitored with an infrared eye-tracking system (ISCAN, Burlington, MA), and the monkeys were required to keep their gaze within 1.75° of the fixation target throughout the trial until the test stimulus appeared. After 500 msec of fixation, a sample stimulus (500 msec) indicated the reference magnitude value, which the monkeys had to remember until the end of the trial. Next, after a 1000-msec Delay 1 period, a rule cue (500-msec duration) instructed the monkeys to apply either the "greater than" rule or the "less than" rule. During a second delay (Delay 2, 1000-msec duration), the monkeys had to remember the type and value of the sample stimulus and the cued rule, to then respond in the Test 1 phase (1200 msec). In this period, the monkeys were required to release the response bar if the "less than" rule had been cued and the displayed magnitude value of the Test 1 display was shorter/smaller than the reference value shown in the sample phase. They had to keep holding the response bar if the Test 1 display was longer/larger than the reference magnitude value when the "less than" rule was cued. Conversely, if the "greater than" rule had been cued, the monkeys were required to respond when the test value was longer/larger and to withhold the response when the test value was shorter/smaller than the sample value. In 50% of the trials (match trials), the magnitude value in the Test 1 period

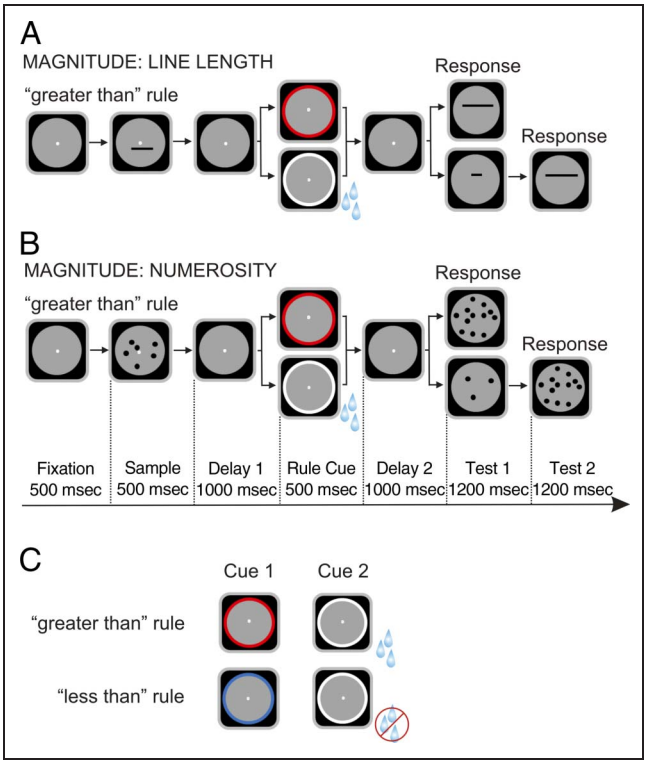

Figure 1. Behavioral task. Two rule-guided magnitude comparison tasks, one based on the length of lines (A) and the other based on the number of dots (B), were presented during each session. (A) Rule-based discrimination task applied to magnitude "line length." After grabbing a response bar and maintaining fixation, a sample line length was presented followed by Delay 1 phase. Next, a rule cue instructed the monkey to apply the appropriate rule ("greater than" or "less than"). Then, after a second delay (Delay 2), a test line length (Test 1) was presented. If the test line length was longer than the sample length and the "greater than" rule was cued, the monkey had to release the bar to be rewarded. If the "less than" rule was cued, the monkey was required to keep holding the bar until in Test 2 phase a shorter line was displayed. Vice versa for the "greater than" rule. Three different sample lengths were shown. (B) Same rule-based discrimination task as in (A), but applied to magnitude "numerosity." Monkeys had to judge whether the test numerosity is smaller or larger than the sample numerosity based on the rule. Three different sample numerosities were shown. (C) Rule cue stimuli. Each rule was indicated by cues of two different sensory modalities. A red circle or white circle with water instructed the "greater than" rule. A blue circle or white circle without water instructed the "less than" rule.

matched the cued rule; in the other half of the trials (nonmatch trials), the magnitude value did not match the cued rule; hence, the monkeys needed to wait and only release the response bar when the second test display (Test 2) was presented. All relevant features (e.g., spatial and numerical magnitude, "greater than" and "less than" rule, rule cue modality, sample magnitude values) were randomized and balanced across trials.

We tested line length stimuli with line lengths of 1.2° of visual angle (shorter test line length = 0.75°, longer test line length = 2°), 2° (1.2°, 3.2°), and 3.2° (2°, 5°) and sample numerosities 3 (*smaller test numerosity* = 1, *larger test numerosity* = 6), 6 (3, 12), and 12 (6, 24). The size and position of each line/dot was randomized, and all stimuli were generated anew for each recording session using MATLAB (MathWorks, Natick, MA). We used control magnitude stimuli (dot density and total pixel area controlled) and generalization trials to ensure that the monkeys solved the task based on the relevant quantitative information and followed an abstract "greater than/less than" principle, irrespective of the individual magnitude types and values (for details, see Eiselt & Nieder, 2013). The rule cues were presented in two different sensory modalities (Figure 1C) to dissociate the rule-related cellular responses from responses to solely sensory features of the rule cue. A red circle or a white circle delivered with a drop of water indicated the "greater than" rule, whereas a blue circle or a white circle delivered with no water cued the "less than" rule.

Electrophysiological Recordings

We recorded extracellular single-cell activity in monkeys equipped with two recording chambers from three areas simultaneously: the right PFC, the left dPMC, and in the left cingulate sulcus from parts of the dorsal CMA (CMAd) and rostral CMA (CMAr). PFC recordings were centered around the principle sulcus. In Monkey E, recording sites were located ventral to the principal sulcus (corresponding to area 9/46v), whereas the majority of recording sites of Monkey O were located dorsal to the principal sulcus (corresponding to areas 9/46d and 45; Petrides & Pandya, 1999). The CMA recordings were made just below the dPMC recording sites at depth ranging from 7.5 to 10.5 mm below cortical surface. We recorded from two behaving rhesus monkeys using two arrays of eight glass-coated tungsten microelectrodes of 1-MΩ impedance (Alpha Omega). Electrodes were inserted each recording day by using a grid with 1-mm spacing. Neurons were selected at random; there was no attempt to preselect neurons according to task-related activity. To access the respective cortex structures, recording chambers were implanted according to stereotaxic coordinates and were reconstructed using MRI images of both monkeys. Signals were amplified, filtered, digitized, and stored for off-line sorting using a Multichannel Acquisition Processor (Plexon, Dallas, TX). Spike sorting was performed off-line and mainly based on PCA and close visual inspection of the entire waveform for each cell (Off Line Sorter, Plexon).

Data Analysis

We used MATLAB (MathWorks, Natick, MA) for all analyses and statistical tests. Because we were interested in the neural activity corresponding to the different magnitude rules, we analyzed the neural activity during the second delay (Delay 2; see Figure 1A, B). In this period, the monkeys are informed about the rule to apply but cannot yet prepare a motor response. Thus, all neural data analysis used a 700-msec time window starting 500 msec after rule cue offset (see Eiselt & Nieder, 2013), except where stated otherwise. The discharge rates were analyzed separately for the two different magnitude types using a three-way ANOVA ($p < .01$) with main factors Rule ("greater than" or "less than"), Rule Cue Modality (visual or tactile), and Sample Magnitude Value (smallest, median, or largest value per magnitude type). We defined rule-selective neurons as cells that showed a significant effect for main factor Rule to one of the two magnitude types (separately tested for each magnitude type, $p < .01$) and had no interaction with the other main factors. We only included neurons with mean firing rates above 1 Hz.

To investigate the effect size of rule selectivity in each brain area, we calculated omega-squared percent explained variance (ω^2 PEV) for each single neuron using a factorial two-way design including the interaction term. The ω^2 PEV calculates how much variability in the neural firing rates can be explained by a specific group membership or variable (e.g., rule) and represents the ratio of the variance between groups and the total variance (Hentschke & Stuettgen, 2011). It is advantageous in that it estimates the population effect size at small sample sizes. Values of zero indicate that the variability of the neural data contains no information about the selected factors. We calculated the time course of ω^2 PEV with a sliding window (100 msec in 20-msec steps) starting at the onset of the rule cue until 100 msec after Delay 2 offset, using the MES toolbox for MATLAB (Hentschke & Stuettgen, 2011) for the variables Rule Cue Modality and Rule. This calculation was based on all recorded neurons separately and then averaged across neurons in each area. Next, we compared the ω^2 PEV of the factor Rule in a time window of 400 msec in the second half of the Delay 2 period (starting 700 msec after rule cue offset) with rule information contained during the fixation period (baseline). The factor Modality was compared either within the same 400 msec time window in the second delay or during the rule cue period (400-msec duration, 100 msec offset after rule cue onset) with the baseline ω^2 PEV during fixation. Values of ω^2 PEV's greater than three standard deviations from baseline ω^2 PEV were considered significant.

Assuming both magnitude types (line length, numerosity) as independent, we used a binomial test to investigate

whether the observed probability of rule-selective neurons that encoded the quantitative rules applied to both magnitude types simultaneously, occurred more often than expected by chance. We then tested, whether each rule generalizing cell (called "generalists") showed rule preference congruency (i.e., preferred the same rule for both quantity types). To estimate the coding quality of rule-selective neurons in each area, we used a receiver operating characteristic (ROC) analysis (Green & Swets, 1966) and calculated the area under the ROC curve (AUROC). The AUROC value determines how well a given neuron discriminates based on discharge rates between the two rules; an AUROC of 0.5 indicates no discrimination, a value of 1 signifies complete discrimination. The temporal evolution of individual neurons' rule selectivity was computed using a sliding window ROC analysis with a 100-msec window moved in 20-msec steps across the rule cue, Delay 2, and beginning of Test 1 period either pooled for each area or for both magnitude types within each area. A permutation test for each individual neuron determined the cells' rule latency: In a sliding window analysis, we calculated the null distribution by shuffling the distribution of firing rates for the "greater than/less than" conditions for each individual neuron (with 1000 repetitions, $p < .05$) and assigned them anew to either category ("greater than" vs. "less than"). If three consecutive time windows showed significant p values and thus exceeded the 95% upper threshold of the null distribution, the neuron's rule latency was determined as the time point of the first significant analysis window. Rule latency could not be determined in four PFC cells (for details, see Eiselt & Nieder, 2013). To compare mean AUROC values between generalists and specialists, we averaged the mean of the generalists' AUROC values of both magnitudes to obtain one AUROC value for each cell.

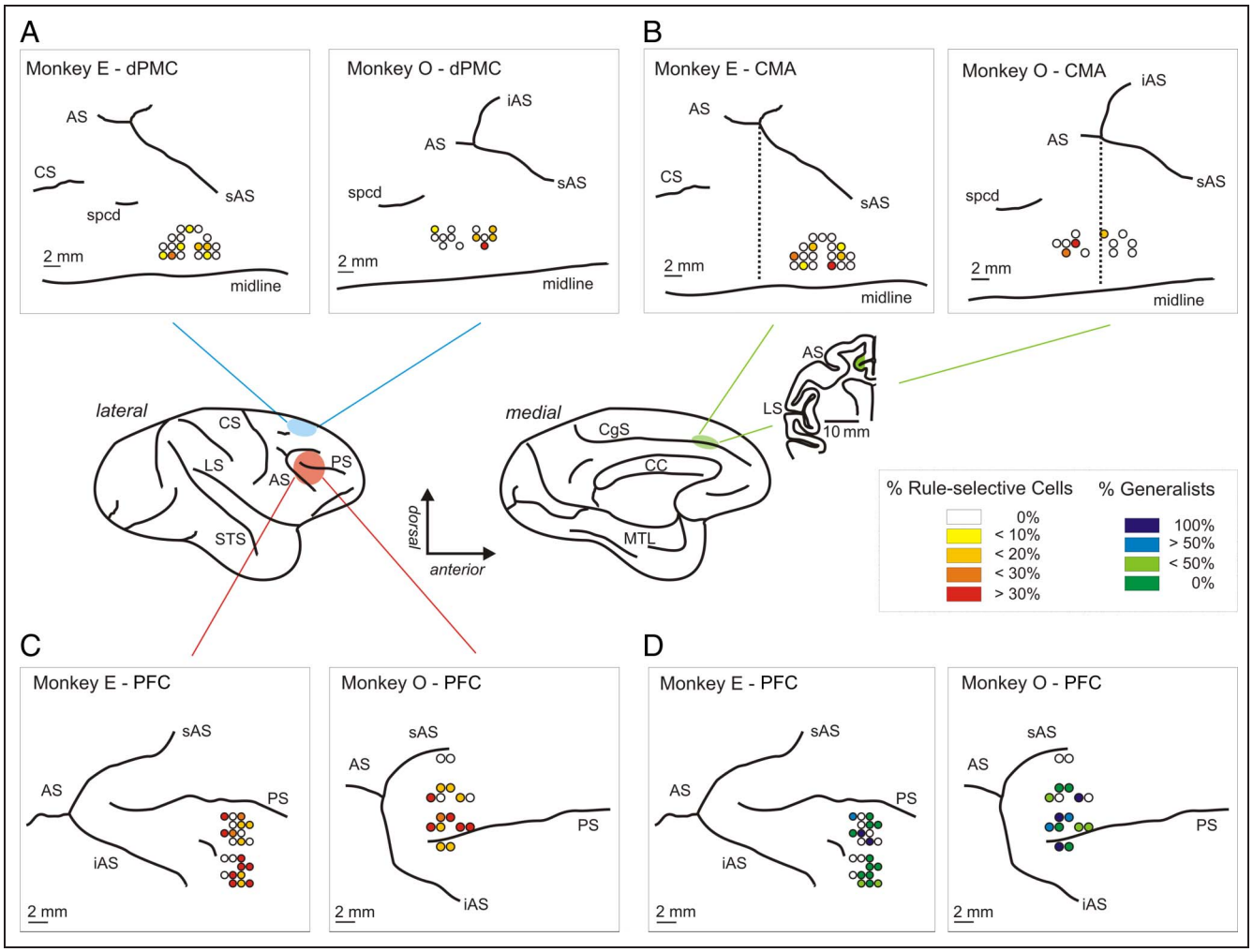

Figure 2. Anatomical locations of recording sites of two monkeys. The middle panel shows lateral (left) and medial (middle) views of a monkey brain, together with a frontal section at the level of the CMA (right). The general locations of recordings are color shaded. (A–C) Recording sites and location of rule-selective cells (color-coded) during the Delay 2 phase for Monkey E and Monkey O in the (A) dPMC, (B) CMA, and (C) pFC. Dotted line indicates the genu of the arcuate sulcus. (D) Recording sites and distribution of generalists and specialists in the pFC for both monkeys. One hundred percent generalists correspond to zero percent specialists and vice versa. AS = arcuate sulcus; CC = corpus callosum; CgS = cingulate sulcus; CS = central sulcus; iAS = inferior limb of AS; LS = lateral sulcus; MTL = medial-temporal lobe; PS = principal sulcus; sAS = superior limb of AS; spcd = superior precentral dimple; STS = superior temporal sulcus.

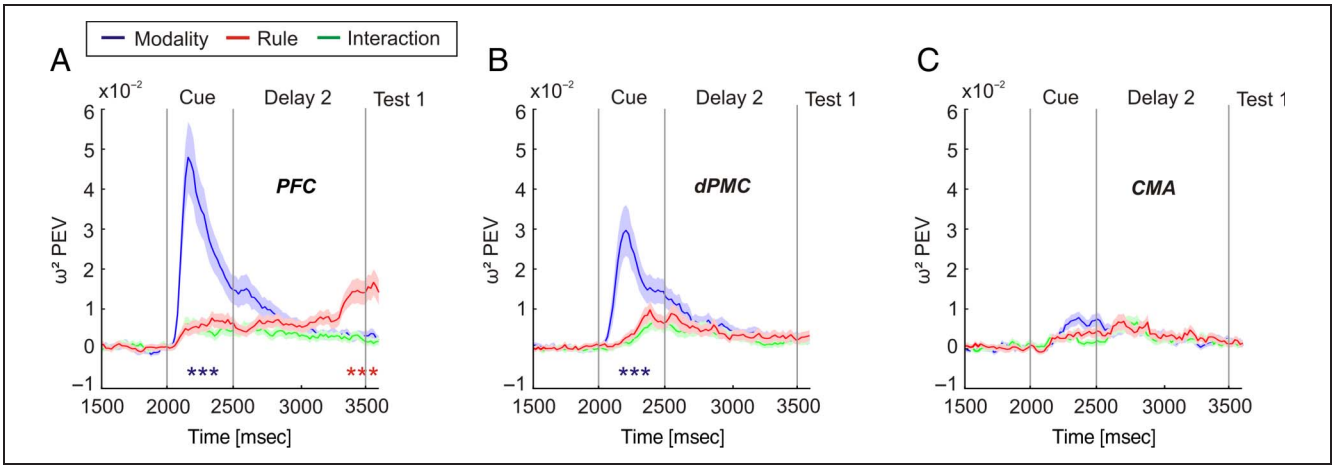

Figure 3. Average percent explained variance (ω^2 PEV) of neuronal discharges in all recorded neurons explained by rule cue modality and rule. Average variability explained by Rule Cue Modality (blue), Rule (red), or Rule Cue Modality × Rule interaction (green) during the rule cue and Delay 2 period for all recorded neurons in (A) pFC, (B) dPMC, and (C) CMA. 2000 msec corresponds to onset of rule cue; baseline activity is plotted for 500 msec before the onset of the rule cue (during the second half of delay 1 period). Asterisks indicate average percent explained variance greater than three standard deviations above baseline ω^2 PEV (separately calculated during the fixation period for either rule cue modality, rule, or their interaction).

To investigate the firing properties of rule-selective neurons in trials displaying the preferred and antipreferred rule, we calculated the normalized firing rate of the preferred and antipreferred rule for which the neuron was selective (e.g., numerosity). We then computed the normalized firing rate of the mean of the nonselective "greater than" and "less than" rules (e.g., line length) as the comparison value. This computation was only valid for specialists, because they obtain a nonselective magnitude type (as opposed to generalists, which are selective for both magnitude types). Normalized activity was derived by subtracting the minimum firing rate and dividing through the sum of the maximum and minimum firing rate for each condition. We then plotted the mean activity of the nonselective magnitude type ("greater than"/"less than" activity of, for example, line length) against the preferred or antipreferred activity to evaluate whether rule-related neural firing rate was elevated, suppressed, or unmodulated.

RESULTS

We trained two monkeys to switch between "greater than/less than" rules applied to line length (innumerable spatial magnitude) and numerosity (countable numerical magnitude; Figure 1) while recording the activity of randomly selected single cells in different cortical areas: the PFC, the dPMC, and the CMA. Both monkeys successfully learned to apply the quantitative "greater than" and "less than" rules to the two different magnitude types and were able to flexibly choose the smaller or larger magnitude value for either the spatial or numerical magnitude. All performance rates for the line length and numerosity stimuli were significantly above chance level ($p < .001$, binomial test; mean performance across conditions was above 90% for both monkeys) and comparable for the two rules (greater than vs. less than), two rule cue modalities (red/blue vs. water/no water), and the two magnitude types (line length vs. numerosity; for detailed behavioral results and generalization trials, see Eiselt & Nieder, 2013).

Overall, we recorded and analyzed 729 neurons from both monkeys: 284 neurons from PFC, 289 neurons from dPMC, and 156 neurons from the CMA. A detailed anatomical map of the recording sites for each monkey and each area is shown in Figure 2. The anatomical locations of the recordings sites from the lateral PFC were slightly different between monkeys (see Methods; Petrides & Pandya, 1999); however, the proportions of rule-selective neurons in PFC of both monkeys were comparable (chi-square test, $p > .05$), and thus, we pooled the data. Recording sites in dPMC were lateral to the medial wall; the most anterior recording sites in dPMC of Monkey E might overlap with the supplementary eye field. In CMA of Monkey O, we recorded approximately half of the neurons anterior (CMAr) and the other half posterior (CMAd) to the level of the genu of the arcuate sulcus (Figure 2B, dotted line), whereas only CMAr neurons were sampled in Monkey E. The number of rule-selective neurons in CMAr and CMAd was indifferent (chi-square test, $p > .05$), so we pooled all neurons in this area.

Selectivity to Quantitative Rules

To investigate potential rule selectivity at the level of the entire populations of neurons in the respective areas, we calculated the omega-squared percent explained variance (ω^2 PEV) statistic for all recorded neurons in each area (Figure 3) for the factors "rule cue modality" and "rule." In PFC, there was an initial increase in explained variance of the rule cue modality after rule cue presentation

(Figure 3A). During the second part of the Delay 2, however, the variance explained by the rule exceeded that of the rule cue modality, indicating that rule information evolves particularly in the late Delay 2 period. This increase in rule coding information was significant compared with rule information contained in the baseline period (exceeded three times the standard deviation of baseline ω^2 PEV; see Data Analysis for details). However, in dPMC no significant rule information was present during the Delay 2 phase, that is, no variance in the neuron's firing rates was explained by the rule in the Delay 2 period; only significant cue modality information during the cue period was observed (Figure 3B). In CMA, there was neither significant rule cue modality information in the rule cue period nor rule information in the second delay (Figure 3C).

Table 1. Percentage and Number (in Parenthesis) of Task-related Neurons Sorted by Main Factors and Interactions for Each Recorded Area

	Numerosity Specialists	*Line Length Specialists*	*Generalists*	*All*
PFC (n = 284)				
Rule	6% (17)	10.9% (31)	8.4% (24)	25.4% (72)
Sample	2.8% (8)	5.3% (15)	0.7% (2)	8.8% (25)
Modality	4.6% (13)	3.5% (10)	1.8% (5)	9.9% (28)
Sample × Rule	2.1% (6)	1.1% (3)	0% (0)	3.2% (9)
Sample × Modality	2.5% (7)	1.1% (3)	0% (0)	3.5% (10)
Rule × Modality	2.8% (8)	2.1% (6)	0.7% (2)	5.6% (16)
Sample × Rule × Modality	1.8% (5)	1.8% (5)	0% (0)	3.5% (10)
Rule-selective cells without any interaction with main factors	**4.9% (14)**	**10.9% (31)**	**8.1% (23)**	**23.9% (68)**
dPMC (n = 289)				
Rule	4.8% (14)	2.8% (8)	1.7% (5)	9.3% (27)
Sample	2.1% (6)	1.7% (5)	0% (0)	3.8% (11)
Modality	4.2% (12)	3.8% (11)	0.7% (2)	8.7% (25)
Sample × Rule	1% (3)	1.4% (4)	0% (0)	2.4% (7)
Sample × Modality	1.4% (4)	1.4% (4)	0% (0)	2.8% (8)
Rule × Modality	3.1% (9)	2.8% (8)	1.7% (5)	7.6% (22)
Sample × Rule × Modality	1.4% (4)	1% (3)	0% (0)	2.4% (7)
Rule-selective cells without any interaction with main factors	**4.2% (12)**	**1.7% (5)**	**0.7% (2)**	**6.6% (19)**
CMA (n = 156)				
Rule	1.9% (3)	3.8% (6)	0.6% (1)	6.4% (10)
Sample	1.3% (2)	0% (0)	0% (0)	1.3% (2)
Modality	4.5% (7)	1.9% (3)	0.6% (1)	7.1% (11)
Sample × Rule	2.6% (4)	1.3% (2)	0% (0)	3.8% (6)
Sample × Modality	0.6% (1)	1.9% (3)	0% (0)	2.6% (4)
Rule × Modality	0.6% (1)	3.2% (5)	0% (0)	3.8% (6)
Sample × Rule × Modality	1.9% (3)	1.3% (2)	0% (0)	3.2% (5)
Rule-selective cells without any interaction with main factors	**1.9% (3)**	**3.2% (5)**	**0.6% (1)**	**5.8% (9)**

Table 1 groups neurons based on their main factors and interactions in the three-way ANOVA ($p < .01$) during the analysis interval. Proportions are based on all recorded neurons in each area. Note that for all reported analyses we used rule-selective neurons that had no interaction with the Sample or Rule Cue Modality (in **bold**).

Next, we analyzed rule selectivity at the level of discharge rates of single neurons. Rule-selective neurons showed significant higher firing rates to either the "less than" or "greater than" rule and had no interaction with the other main factors Sample and Rule Cue Modality in the second half of the Delay 2 period (three-way ANOVA, $p < .01$). Thus, these rule-selective cells were abstractly encoding quantity rules and were independent of any other sample or rule cue effect in the analyzed time window. A detailed summary of the results obtained by the three-way ANOVA is listed in Table 1. We previously reported that 23.9% of all recorded PFC neurons (68/284) showed significant rule coding (Eiselt & Nieder, 2013). Such rule-selective neurons had a significant effect of the factor rule, but no interaction with the factors sample or rule cue modality. In dPMC, however, only 6.6% of all recorded neurons (19/289) encoded the rule and a similar fraction of CMA neurons, 5.8% (9/156), was rule selective. A similar number of rule-selective neurons was found (dPMC: 22 cells; CMA: 11 cells) when calculating a three-factor ANOVA with main factors Magnitude Type (numerosity, line length), Rule (greater than, less than), and Cue Modality (visual, tactile) in all recorded neurons in dPMC and CMA. Thus, significantly more rule-selective neurons were present in PFC (24%) compared with dPMC (6.6%) and CMA (5.8%; $p < .01$, chi-square test).

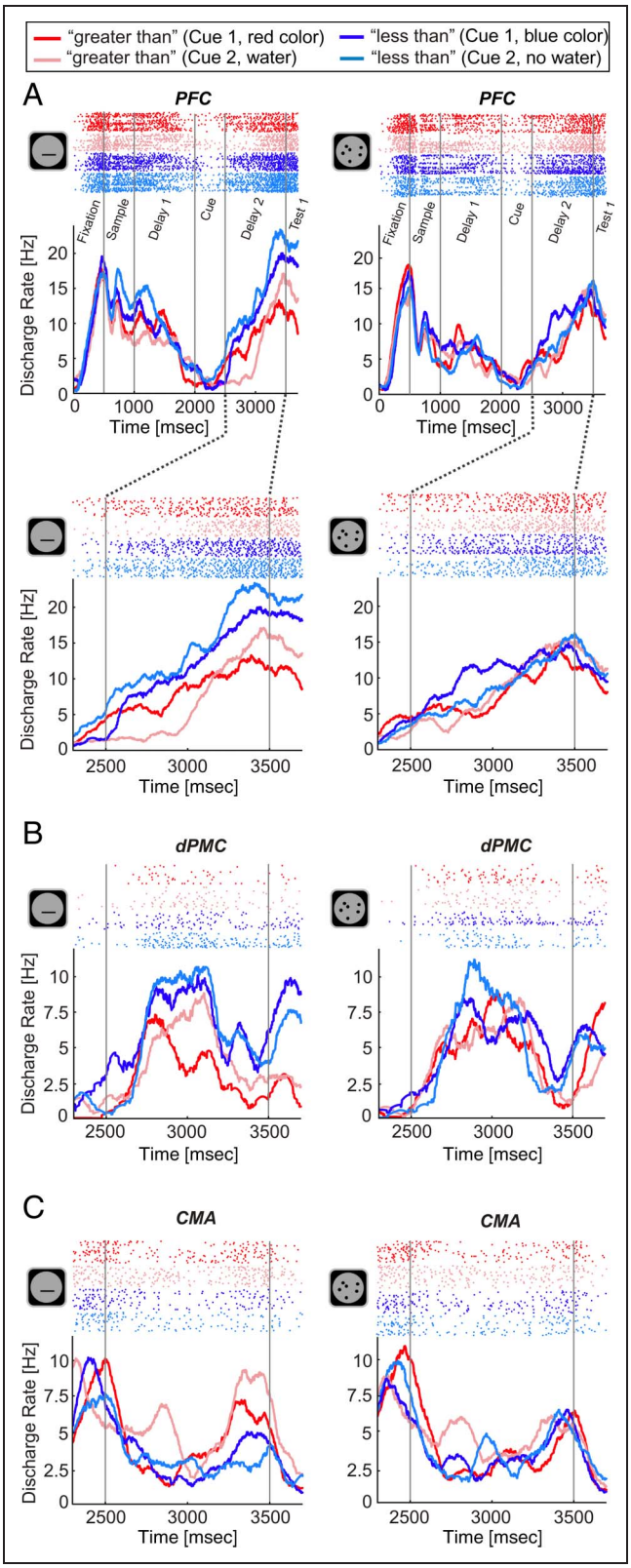

Figure 4. Examples of rule-selective cells from different frontal brain areas. (A) Example of a pFC rule specialist. A neuron encoding the rule only for line lengths (left), but not for numerosities (right). Raster displays show spike times (each dot represents an action potential, spike trains are sorted and color-coded according to the rules and rule cues) with spike density averages below (activity averaged over all trials and smoothed by a 150-msec Gaussian kernel). Top panel depicts the whole trial; bottom panel depicts rule cue, Delay 2, and beginning of Test 1 phase. (B) A dPMC rule specialist encoding the rule only for line length stimuli (left) and not for numerosities (right). (C) A CMA rule specialist that was rule selective when the rule was applied to line length, but not when the rule was applied to numerosity.

Rule Coding of Multiple Magnitude Types

Of all recorded cells in PFC, a proportion of 19% (54/284) was significantly selective to the rules applied to line length and 13% of all recorded neurons (37/284) responded to the rules related to numerosity. In dPMC, only 2.4% of all recorded neurons (7/289) were selective for line length rules and 4.8% (14/289) were selective for numerosity rules. A similar fraction of 3.8% of all recorded neurons in CMA (6/156) responded significantly to rules applied to line length and 2.6% (4/156) to rules applied to numerosity stimuli. In all three recorded areas, the number of neurons responsive to rules applied to either numerosity or line length did not differ ($p > .05$, chi-square test). Approximately half of the rule-selective neurons preferred the "greater than" rule (PFC: 34/54 for line length, 19/37 for numerosity; dPMC: 3/7 for line length, 6/14 for numerosity; CMA: 3/6 for line length, 3/4 for numerosity), whereas the other half preferred the "less than" rule ($p > .05$, binomial test). The responses of example rule-selective neurons from each of the three recorded areas that encode the rule for line

length stimuli are shown in Figure 4A–C. Each cell significantly differentiated between the "greater than/less than" rule after the rule cue was given, but only did so for the line length magnitude, not when numerosity stimuli were shown. Thus, these neurons were specialists, preferring either the less than (Figure 4A, B) or greater than rule (Figure 4C) only when line length stimuli were presented.

Rule Generalists versus Rule Specialists

In PFC, we previously found with separate ANOVAs applied to numerosity and line length responses that a significant proportion of 34% of all rule-selective cells (23/68) encoded quantitative rules applied to both magnitude types (line length and numerosity). The number of so-called "rule generalists" was higher than expected by chance ($p < .001$, binomial test). In addition, "greater than/less than" rule activity was congruent for both magnitudes in almost all "rule generalist" neurons (22/23, $p < .001$, binomial test; Eiselt & Nieder, 2013). In other words, a neuron discharging higher to the "greater than" rule in the numerosity protocol also preferred the "greater than" rule in the line length task. Almost the same number of "rule generalists" was found ($n = 21$) when calculating an additional three-factor ANOVA across magnitude types (main factors Magnitude Type, Rule, and Cue Modality) for all rule-selective cells. The other 66% (45/68) of the 68 rule-selective cells in PFC encoded only rules to one specific magnitude type (applied either to line length or numerosity) but were indifferent for the other magnitude. We called such rule-selective neurons "rule specialists."

In dPMC, only two of all rule-selective neurons (2/19, 11%) were rule generalists, whereas 89% of all rule-selective cells (17/19) encoded the rule always in conjunction with a specific magnitude. Both of these generalists in dPMC showed congruent rule preference for each magnitude type. However, the binomial test to investigate whether more dPMC neurons than expected by chance were encoding the rules for both magnitude types barely reached significance level ($p = .05$, binomial test). In light of the very small proportions of the rule-selective neurons for the line length (7/289) and numerosity magnitude (14/289), the conclusion that rule generalists are more frequent than expected by chance in PMC would be premature. Similarly, almost all rule-selective cells in CMA were specialists (8/9, 89%), so the number of generalists (1/9, 11%) was indifferent from chance expectation ($p > .05$, binomial test). Figure 5A summarizes the

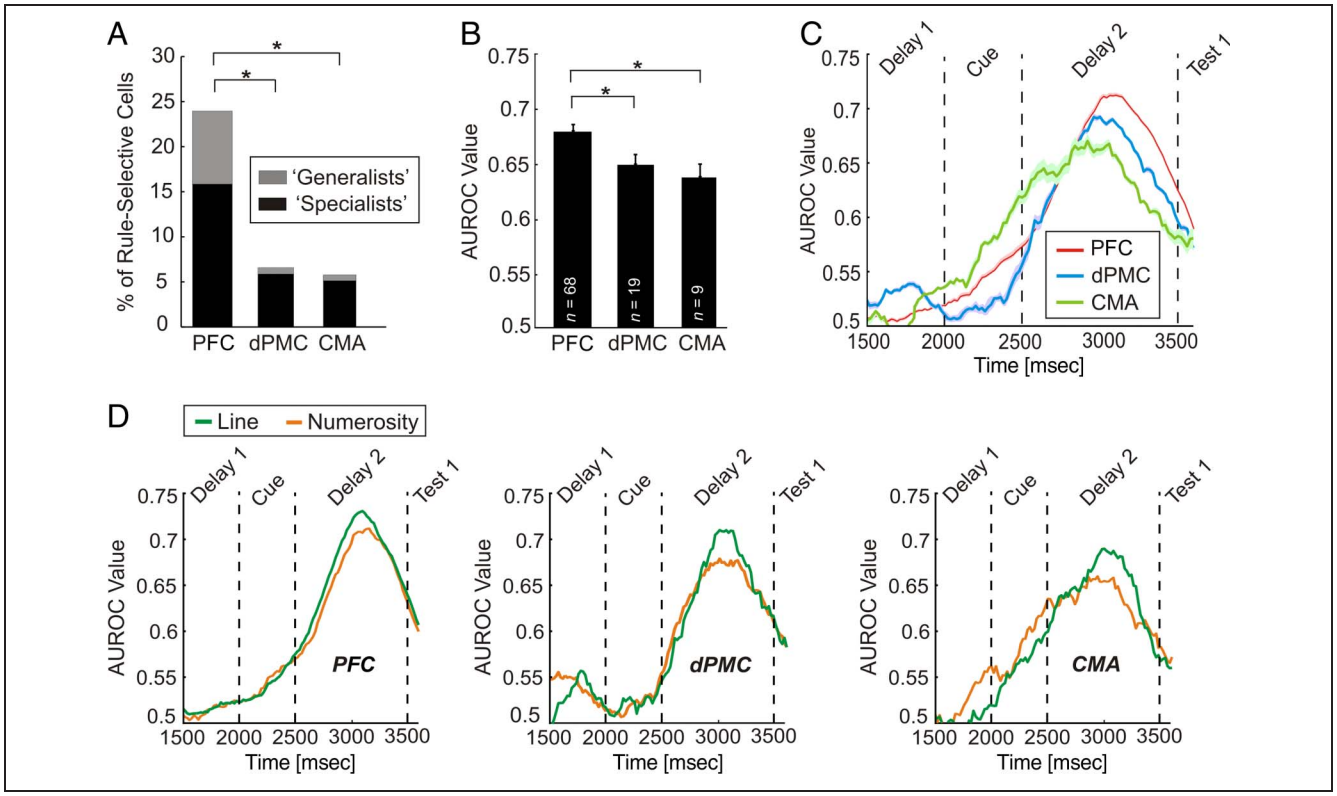

Figure 5. Differences in rule selectivity between areas. (A) Percentage of rule-selective cells and distribution of generalists and specialists in all three areas. Asterisks indicate $p < .01$. (B) Mean AUROC values for all rule-selective cells of each area. (C) Temporal evolution of mean AUROC values in the rule cue and Delay 2 phase for all three areas using a sliding window AUROC analysis. (D) Temporal evolution of mean AUROC values in the rule cue and Delay 2 period for cells rule-selective for line length (green) or numerosity stimuli (orange) in pFC (left), dPMC (middle), and CMA (right). 2000 msec indicates onset of rule cue; baseline activity is plotted for 500 msec before the onset of the rule cue (during the second half of Delay 1 period).

percentage of rule-selective generalists and specialists in the three areas.

Rule Coding Quality in Different Cortical Areas

Next, we characterized the quality of rule selectivity using an ROC analysis in the same 700 msec time window at the end of the Delay 2 phase as used for the ANOVA. We calculated the area under the curve (AUROC) values for each cell, which could range from 0.5 (indicating no rule information) to 1 (which corresponds to perfect rule discrimination). The coding quality (based on the mean AUROC values) was significantly better in PFC (mean AUROC = 0.68) compared with dPMC (0.65) and CMA (0.64; $p < .05$, Mann–Whitney U test; Figure 5B). There were no differences in AUROC values for "greater than" and "less than" neurons for the line length (mean AUROC PFC = 0.71 and 0.74, respectively; mean AUROC dPMC = 0.69 and 0.71, respectively; mean AUROC CMA = 0.73 and 0.63, respectively) and numerosity stimuli (PFC = 0.70 and 0.71, respectively; dPMC = 0.68 and 0.67, respectively; CMA = 0.65 both; for all comparisons $p > .05$, Mann–Whitney U test). This overall difference in AUROC values between areas was especially present in the second half of the Delay 2 phase as can be seen in Figure 5C, which depicts the AUROC value as a function of time starting at the second half of the Delay 1 period using a sliding window ROC analysis.

A comparison of the value under the curve (i.e., integral) for each neuron showed that the temporal evolution of AUROC values for line length and numerosity rule-selective cells (Figure 5D) were comparable within each area ($p > .05$, Mann–Whitney U test). To compare

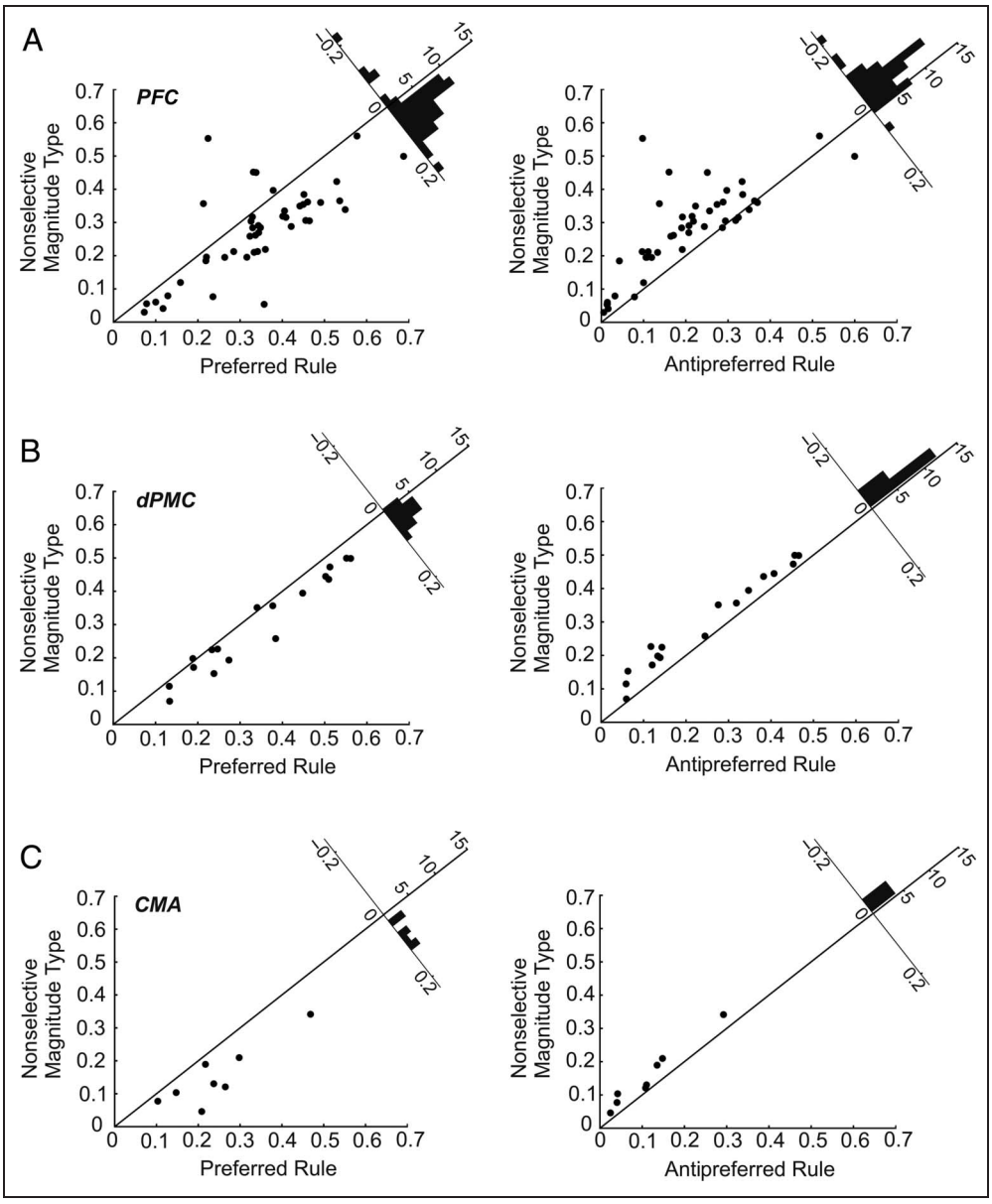

Figure 6. Discriminability between preferred and antipreferred rules based of firing rates. Comparison of firing rates of each rule-selective neuron for the preferred rule (left) and antipreferred rule (right) compared with the nonselective magnitude type (e.g., line length or numerosity) for (A) pFC, (B) dPMC, and (C) CMA. Values below diagonal indicate elevation of firing rate of selective rules (e.g., "greater than" for line length) compared with the firing rate during nonselective rule presentation (e.g., "greater than" and "less than" rules for numerosity). Values above diagonal indicate suppression of firing rate for selective rules compared with the firing rate during nonselective rules. Histograms indicate number of neurons above or below diagonal.

rule latencies between and within areas, we calculated a sliding window AUROC analysis and used a permutation analysis ($p < .05$, permutation test; see Data Analysis for details). There were no latency differences between rule-selective cells of the three areas nor between numerosity and line length rule-selective cells within each area ($p > .05$, Mann–Whitney U test, latency could not be determined in four PFC neurons).

Because of the high performance rate of both monkeys, we recorded only very few neurons with a sufficient number of error trials in PFC ($n = 9$), dPMC ($n = 3$), and CMA ($n = 1$). A comparison of rule-selective activity in error trials between these areas was therefore precluded. Although the behavioral relevance of rule coding activity in PFC is established (Eiselt & Nieder, 2013), the role of dPMC and CMA cells in our study remains elusive.

Active Elevation and Suppression of Rule Selective Activity

Next, we investigated the mechanism of how the discriminability between preferred and antipreferred rules was implemented based on the discharge rates. One possibility is that the firing rate of a single neuron to the preferred magnitude rule (e.g., "greater than" line length rule) is elevated above the mean firing rate of that neuron to the nonselective magnitude rules (e.g., mean of "greater than/less than" rules for numerosity). A second possibility is that the antipreferred magnitude rule (e.g., "less than" rule for line length stimuli) is suppressed below the mean firing rate to the nonpreferred magnitude rules (e.g., mean of "greater than/less than" rules for numerosity). To enlarge the firing rate difference between preferred and antipreferred magnitude rule, it could also be both: an elevation of firing rate of the preferred magnitude rule and a suppression of firing rate to the antipreferred magnitude rule. Figure 6 shows the normalized firing rate to the preferred magnitude rule (left) and antipreferred magnitude rule (right) against the mean of the nonselective magnitude rules for each cell in PFC (Figure 6A), dPMC (Figure 6B), and CMA (Figure 6C). Values above the diagonal indicate lower firing rate compared with the nonselective magnitude rules, whereas values below the diagonal indicate higher firing rate compared with nonselective magnitude rules. Histograms count the number of cells either above or below the diagonal. For all areas, the elevation (for the preferred rule) and suppression (for the antipreferred rule) of firing rates for all rule-selective specialists (only specialists are shown, because generalists prefer both numerosity and line length, so there are no nonselective magnitude rules) was significantly different from the diagonal ($p < .01$, Wilcoxon signed rank test). This indicates that the firing rate to the preferred rule was elevated above the mean of the nonselective magnitude rule firing and that the firing rate to the antipreferred rule was suppressed below the mean of the nonselective magnitude rule firing.

DISCUSSION

In this study, we compared abstract rule-related activity in three different frontal areas of the cortex (lateral PFC, dPMC, and CMA) while monkeys had to flexibly switch between quantitative rules applied to two different magnitude types. We found most rule-selective cells in PFC (24%), whereas in dPMC and CMA only around 6% of all recorded cells encoded the rule. Additionally, these rule-selective neurons in PFC encoded the rule significantly stronger compared with dPMC/CMA neurons. Furthermore, rule generalists, which are encoding the rule for line length and numerosity stimuli simultaneously, were exclusively present in PFC with a proportion of 34% of all rule-selective prefrontal cells. In dPMC and CMA, however, we did not find more generalizing cells than expected by chance. The rare rule-selective neurons in dPMC and CMA were almost solely specialists, indicating that generalizing/multitasking neurons are a unique feature of PFC.

Role of PFC in a Frontal Network Encoding Quantitative Rules

Many studies, including lesion and inactivation studies, suggested a special role of PFC neurons in flexible, rule-based decision-making (Kamigaki et al., 2012; Cromer, Roy, Bushmann, & Miller, 2011; Kim, Johnson, Cilles, & Gold, 2011; Roy et al., 2010; Mansouri, Buckley, & Tanaka, 2007; Hoshi, Shima, & Tanji, 2000; Rainer, Asaad, & Miller, 1998). Several neurophysiological studies indicated a causal role of PFC activity in handling abstract information (Badre, Hoffman, Cooney, & D'Esposito, 2009; Shallice & Evans, 1978; Milner, 1963), and it was shown that PFC is critically involved in strategy-related (Tsujimoto, Genovesio, & Wise, 2012; Tanji & Hoshi, 2008; Mansouri et al., 2007; Genovesio et al., 2005) and rule-based tasks (Kamigaki et al., 2012; Bongard & Nieder, 2010; Buckley et al., 2009; Wallis et al., 2001; White & Wise, 1999). Although different subregions of the lateral PFC have different connectivity patterns and might also represent different functions (e.g., Badre & D'Esposito, 2009; Tanji & Hoshi, 2008; Petrides & Pandya, 1999; Bates & Goldman-Rakic, 1993), we did not observe any differences in coding abstract rules between PFC areas ventral or dorsal to the principal sulcus.

Albeit, PFC might not operate in isolation, and it has been suggested that a wider frontal network is involved in such rule-related tasks (Vallentin et al., 2012; Muhammad et al., 2006; Wallis & Miller, 2003; Brass & von Cramon, 2002; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000). Several studies support the view of a functional cortical network involved in abstract rule guided behavior, with variable contributions of different frontal areas. For example, it has been shown that the PMC receives output signals from the PFC through strong multisynaptic connections (Miyachi et al., 2005; Pandya & Yeterian, 1990; Barbas

& Pandya, 1987, 1989), which suggest a vivid interaction between these areas. Previous findings from our lab (Vallentin et al., 2012) and from others (Muhammad et al., 2006; Wallis & Miller, 2003) suggested that PMC activity might contain even stronger rule signals compared with PFC. However, in our study we find an outstanding role of PFC activity when abstract rules had to be applied to multiple magnitude types. We found almost four times as many rule-related cells in PFC (24%) compared with dPMC (6.6%). This rule-selective activity was also strongest (i.e., highest ROC values) in PFC. Latency difference between PFC and dPMC were absent, which contrasts other findings (Muhammad et al., 2006; Wallis & Miller, 2003). Cromer et al. (2011), on the other hand, found stronger category representation in a visual categorization task in PFC compared with PMC; both the number of category selective neurons and the strength of category sensitivity were higher in PFC, which is in line with our results. The authors also report no latency difference between these areas, which opposes the results from Muhammad et al. (2006) and Wallis and Miller (2003), who found that PMC neurons not only encoded a same/different rule stronger but also earlier than PFC neurons. Compared with the "match/non-match" rule used by Wallis and Miller (2003) and the "same/different" rules used by Muhammad et al. (2006), our task design might comprise a greater task complexity because it involves two rules (greater than, less than) assigned by two different rule cues (rule cue modality) applied to two different magnitude types (line length and numerosity). This could play a potential role in the pronounced recruitment of PFC neurons. In tasks requiring more and more abstract information-response mapping, fMRI activity shifted from dPMC to dorsolateral PFC (Badre & D'Esposito, 2007; Koechlin, Ody, & Kouneiher, 2003), indicating a distinction in the activation of different frontal areas depending on the degree of abstraction of representations or task demands. Thus, as rule-guided behavior becomes more abstract or demanding, more neurons from the lateral frontal lobe (like dorsolateral PFC) might be recruited, which might explain the different results. Besides task differences, PMC recording sites of Muhammad et al. (2006) and Wallis and Miller (2003) were more ventral (just above the genu of the arcuate sulcus), which is different from ours and Cromer et al.'s (2011) recordings in the dorsal part of the PMC. Hence, another possible explanation for these diverging results could be that the dorsal part of the PMC is to a lesser extent involved in rule following than the more ventral part of the PMC (but see Hoshi & Tanji, 2007).

A third important frontal region that might be involved in rule-guided decisions is the cingulate cortex, which also shows strong connections to the PFC (Luppino, Rozzi, Calzavara, & Matelli, 2003; Barbas & Pandya, 1989). Electrophysiological studies suggest that this region is critical for voluntary (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006) and even rule-based decision-making (Vallentin et al., 2012; Womelsdorf et al., 2010; Buckley et al., 2009). Recently, using tract-tracing experiments, Takahara et al. (2012) mapped massive connections between the dorsolateral PFC, dPMC, and rostral cingulated motor areas, which suggests that these areas might share task-related representations.

In the current study, we report a rather small fraction of 5.8% of all recorded cingulate motor neurons that were representing the quantitative rules. However, this proportion of rule-selective neurons in CMA is comparable with Vallentin et al. (2012), who found 7% of all recorded CMA neurons to represent numerical "greater than/less than" rules. Overall, the most prominent rule representation was found in PFC. In dPMC and CMA, quantitative rules applied to two different magnitude types were encoded by a rather small number of neurons and to a weaker extent compared with PFC.

Rule Generalists versus Specialists in Different Frontal Areas

There is ample evidence that PFC plays a particular important role in categorization, rule following, and generalizing these rules and categories (e.g., Pan & Sakagami, 2012; Cromer et al., 2010; Buckley et al., 2009; Shima, Isoda, Mushiake, & Tanji, 2007; Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005; Miller, Nieder, Freedman, & Wallis, 2003). Recent studies (Cromer et al., 2010; Roy et al., 2010; Seger & Miller, 2010) suggest that rather than a hardwired neural network involved in category representation and generalization, the brain might recruit different neural connections to fulfill different functions depending on task demands and context and that PFC neurons might be especially involved when "multitasking" is required.

In our study, we found 34% of all rule-selective neurons in PFC generalizing across magnitude type, which is much more than what would be expected by chance. In dPMC and CMA, however, only very few of such generalists were recorded (2/19 and 1/9 generalist of all rule-selective cells in dPMC and CMA, respectively). Overall, the number of rule-selective cells in these areas encoding the rule either as specialists or by representing the overarching concept of "magnitude rule" (generalists) was so little that any conclusion about the existence of rule generalists in premotor and cingulate motor cortex areas would be premature. Our data indicate that the PFC might be particularly involved in the process of abstraction and generalization, whereas the dPMC and CMA, on the other hand, might not have the potential flexibility to represent quantitative rules applied to multiple magnitude types simultaneously.

Quantitative Rules Applied to Multiple Magnitudes

It has been shown that quantity information is represented most abstractly in the PFC (Nieder, 2009, 2012, 2013; Diester & Nieder, 2007; Nieder et al., 2002). Here we show that abstract rules applied to continuous and discrete quantity information are predominantly represented in

PFC. Within each brain area, magnitude rules applied to either line length or numerosity stimuli were represented indifferent from each other, that is, equally strong and with equal temporal evolution of the coding signal. Hence, the main difference in rule coding applied to multiple magnitude types was between areas (with the largest proportion and strongest rule-selective neurons situated in PFC), as described above. Common to all three brain areas was the mechanism underlying the discriminability of preferred and antipreferred rules. In all three areas, the firing rate for the preferred magnitude rule of one neuron was elevated above the mean response to the nonselective magnitude type of this neuron. The firing rate for the antipreferred magnitude rule, however, was decreased below the mean response to the nonselective magnitude type. This mechanism might enhance the discriminability between the preferred and antipreferred rule. It was present in all three areas and thus seems to be independent of rule coding strength as measured as AUROC values, which were significantly different between areas.

Conclusion

Taken together, the current results suggest that flexibly operating with abstract quantity information might be a unique characteristic of the PFC. In our task, monkeys had to switch between different rules (greater than/less than) and different magnitude types (line length, numerosity). The results suggest that rule switching between "greater than/less than" rules and magnitude types recruited especially the PFC, where we found more and stronger rule-selective cells. In addition, PFC seems to be the only area harboring generalists, which were absent in dPMC and CMA, where rule-selective cells were almost exclusively specialized to a particular magnitude type. Thus, PFC might play a special role in applying quantitative rules to multiple magnitude types, which would favor the idea of PFC as the cardinal processing stage for abstract principles applied to multiple stimulus types.

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Reprint requests should be sent to Andreas Nieder, Animal Physiology, Institute of Neurobiology, University of Tübingen, Auf der Morgenstelle 28, 72076 Tübingen, Germany, or via e-mail: andreas.nieder@uni-tuebingen.de.

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