left-sided omissions indicated spatial neglect. Baking tray task[28]: patients had to place 16 identical items as evenly as possible on a blank test sheet (21 × 29.7 cm). Any distribution that is more skewed than seven items in the left half and nine on the right[28] was considered a sign of neglect. Copying task: patients were asked to copy a complex multi-object scene consisting of four figures on a 21 × 29.7 cm sheet of paper. Omission of at least one of the left-sided features of each figure was scored as one and omission of each whole figure was scored as two. One additional point was given when left-sided figures were drawn on the right side. The maximum score was eight. A score higher than one, that is, more than 12.5% omissions, indicated neglect.

All other relevant demographic and clinical parameters are shown in Table 1, together with an overview of these data. Visual-field defects were measured by Tübingen perimetry and standardized neurological examination.

Lesion analysis

Brain lesions were identified by computerized tomography or magnetic resonance imaging (MRI). Patients with diffuse or bilateral brain lesions, patients with tumours and patients in whom imaging revealed no manifest lesion were excluded. Lesions were mapped with MRIcro software[17] (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). They were drawn manually on slices of a template MRI scan from the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca/cgi/icbm_view), which is based on 27 T1-weighted MRI scans, normalized to Talairach space[16]. This scan was distributed with SPM99 (http://www.fil.ion.bpmf.ac.uk/spm/spm99.html). For superimposing of the individual brain lesions, the same MRIcro software[17] was used. Three-dimensional rendering was carried out with mri3dX software (http://mrrc11.mrrc.liv. ac.uk/mri3dX).

Received 23 January; accepted 25 April 2001.

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Acknowledgements

This work was supported by grants from the Deutsche Forschungsgemeinschaft and the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie awarded to H.-O.K. We thank M. Niemeier, L. Johannsen and U. Zimmer for support with the neuropsychological testing of the patients; P. Thier for discussion and suggestions for the manuscript; U. Amann for help in the tomography archives; and C. Rorden for developing the MRIcro software.

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Single neurons in prefrontal cortex encode abstract rules

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The ability to abstract principles or rules from direct experience allows behaviour to extend beyond specific circumstances to general situations. For example, we learn the 'rules' for restaurant dining from specific experiences and can then apply them in new restaurants. The use of such rules is thought to depend on the prefrontal cortex (PFC) because its damage often results in difficulty in following rules[1]. Here we explore its neural basis by recording from single neurons in the PFC of monkeys trained to use two abstract rules. They were required to indicate whether two successively presented pictures were the same or different depending on which rule was currently in effect. The monkeys performed this task with new pictures, thus showing that they had learned two general principles that could be applied to stimuli that they had not yet experienced. The most prevalent neuronal activity observed in the PFC reflected the coding of these abstract rules.

Neurons in the prefrontal cortex (PFC) encode many different types of information from all stages of the perception–action cycle[2]. They are activated by stimuli from all sensory modalities[3–5], before and during a variety of actions[6–8], during memory for past events[9], in anticipation of expected events and behavioural consequences[10–12], and are modulated by 'internal' factors such as motivational and attentional state[13,14]. The PFC is thought to use this diverse information for the 'higher order' control of behaviour, in particular the application of behaviour-guiding rules that are lost after damage to the PFC[15,16]. Although rules can be specific and concrete (for example, 'red' means 'stop'), it is the abstraction of general rules or principles (those not tied to any particular stimulus or behavioural response) that allows for the flexibility and adaptability that are central to intelligent behaviour. Although recent studies indicate that PFC neurons can encode concrete rules between specific stimuli and behavioural responses[17–19], we do not know how, or even whether, PFC neurons can encode abstract rules.

Thus, we trained two monkeys to switch flexibly between two abstract rules. The 'match' rule required monkeys to release a lever if two successively presented (sample and test) objects were identical, whereas the 'nonmatch' rule required the lever release if the two objects were different (Fig. 1). The rule applicable for each trial was randomly indicated by a cue that was presented with the sample. To separate 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 rules, whereas cues signifying different rules were from the same modality (Fig. 1). Both monkeys were proficient at the task (92% and 84% correct performance) and performed well above chance when applying the rules the very first time they encountered a new object (70% correct, 4 objects × 55 recording sessions = 220 objects; $P < 10^{-8}$; binomial test).

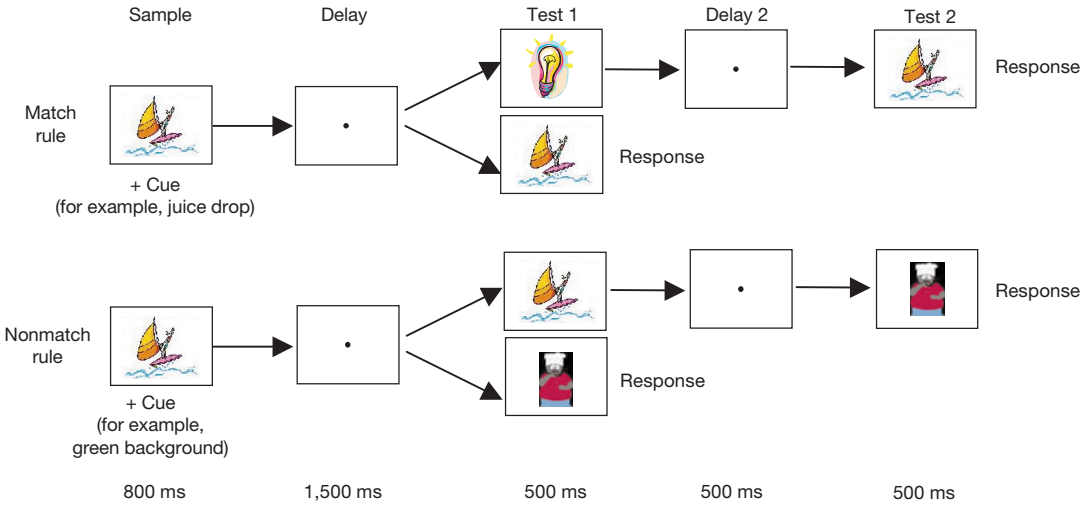

Figure 1 The behavioural task. Monkeys grasped a lever and maintained central fixation. A sample object was followed by a brief delay, and then by only one test object. Illustrated are two trial types for each rule (bifurcating arrows). For the match rule, the monkeys released a lever if the test object matched the sample. For the nonmatch rule, they released the lever if the test object did not match. Otherwise, they held the lever through a second delay until appearance of a second test object that always required a response. Thus, only the first test required a decision; the second delay and test was used so that a behavioural response was required on each trial, ensuring that monkeys were always paying attention.

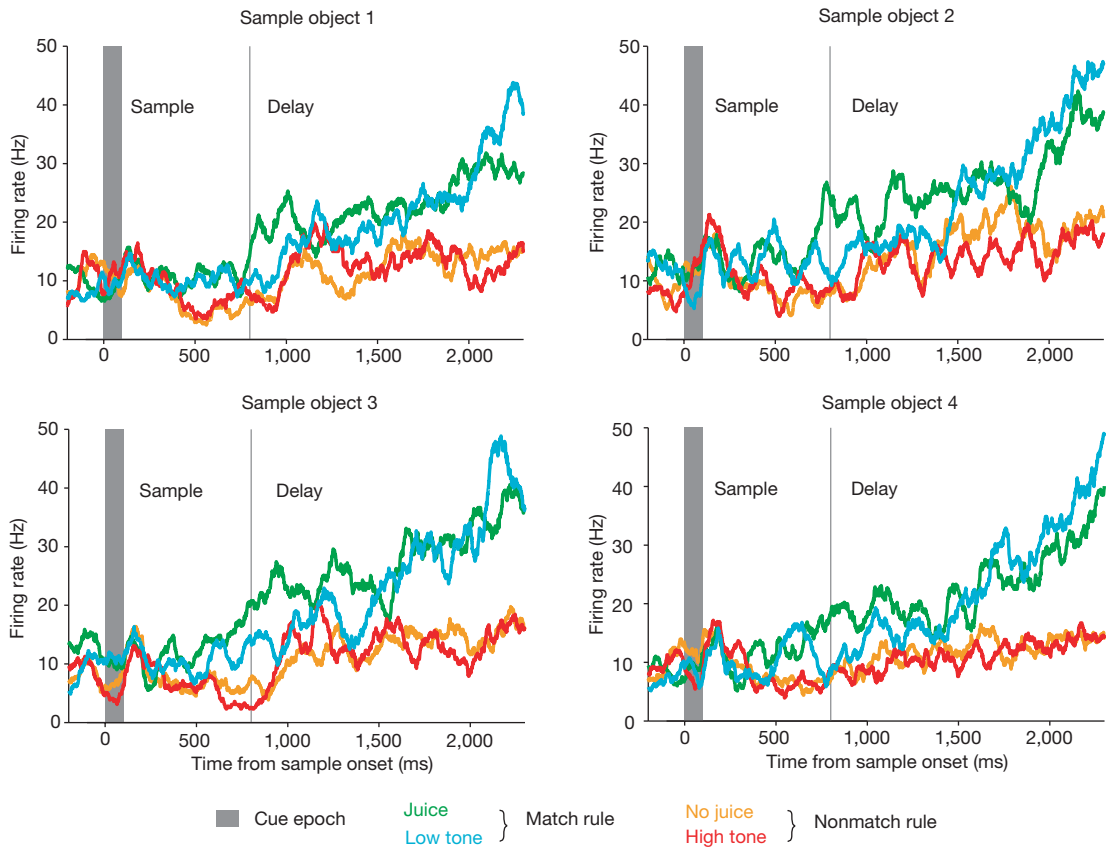

Figure 2 A neuron exhibiting rule selectivity. The neuron shows greater activity during match trials, regardless of which cue signified the rule or which object was remembered. It showed a 72% difference in activity between the rules in the sample epoch and a 120% difference during the delay (0.27 and 0.37 as measured by the selectivity index). The mean firing rate during the delay epoch was 13.2 spikes s^{-1} and the 99% confidence interval was ±0.91) for the nonmatch rule and 24.8 spikes s^{-1} (±1.15) for the match rule.

We recorded the activity of 492 neurons from the dorsolateral, ventrolateral and orbitofrontal PFC. To discern whether neural activity in the sample and delay epochs reflected the cues, sample objects, and/or rules, three-way analysis of variance (ANOVA) tests were computed for each neuron (see Methods). The modal group of PFC neurons showed activity that reflected the current rule (200/492 or 41%; see Table 1). Figure 2 shows a good example of a rule-selective neuron that exhibited greater activity when the match rule was cued. This activity cannot be explained by the physical characteristics of the sample object or cues; activity was equivalent regardless of the specific sample or of which cue signified a given rule. It cannot be related to anticipation of the behavioural response as the monkey could not know if the forthcoming object would require a response. Nor could it be related to differences in reward expectation. Although in one of the conditions the rule was cued with a drop of juice at the beginning of the sample epoch, the expectation of reward was identical for all conditions for the remainder of the trial. Furthermore, performance on match and nonmatch trials was virtually identical (across monkeys, average error rates differed by only 0.1% and reaction times by 7 ms). Thus, the most parsimonious explanation is that the activity reflected the abstract rules that the monkeys were using to guide their behaviour.

Figure 3 shows a distribution of the magnitude of rule-selectivity for the population of rule-selective neurons (see Methods). The mean of their absolute values was 0.18 and 0.13 for the sample and delay, respectively, which corresponds to a 48% and 33% difference in activity for match versus nonmatch rules. The number of neurons that showed stronger activity for the match rule (101/200, or 50.5%) was similar to that of neurons that were more active for the nonmatch rule (99/200, or 49.5%) and the magnitude of rule-selectivity to each did not differ (Wilcoxon rank sum test, $P > 0.05$ in both sample and delay intervals).

The second most prevalent type of neuronal activity observed was a Cue × Rule interaction (167/492 or 34% of neurons), which occurred when a neuron was most active to a single cue. This may simply reflect the physical properties of the cue, although, in principle, it could also carry some rule information—for example, by encoding rule information but only from a single modality. Finally, 14% of the neurons (70/492) showed activity that reflected the identity of the sample object.

To further demonstrate abstract rule representation, pairwise t-tests were made for each neuron between activity to the four cues (yielding six unique comparisons) across both the sample and delay epochs ($P < 0.01$, Bonferroni corrected). Because our task design set cue modality in opposition to rule (two cues from the same sensory modality instructed two different rules and the same rule was indicated by cues from two different modalities) many PFC neurons tended to group cues by modality or rule (Table 1). We adopted a strict criterion to indicate such selectivity: for a given set of cue pairs, there had to be significant differences in all across-pair comparisons (4/6 comparisons) but no significant difference to cues within each of the pairs (2/6 comparisons).Of the 91 PFC neurons that met this criterion, most (69/91 or 76%) grouped the cues by rules. Their activity was significantly different to similar cues that indicated different rules but not significantly different to distinct cues that indicated the same rule. Far fewer neurons grouped the cues on the basis of their modalities (15/91, or 16%) or by neither rule nor modality (6/91 or 6%). Further evidence of supramodal rule-coding is the similar proportion of rule-selective neurons in the two monkeys even though different cue modalities were used for each monkey (125/303 or 41% in monkey A, and 75/189 or 40% in monkey B).

Encoding of abstract rules was evident throughout the PFC (Fig. 4). During the sample epoch there was a higher incidence of

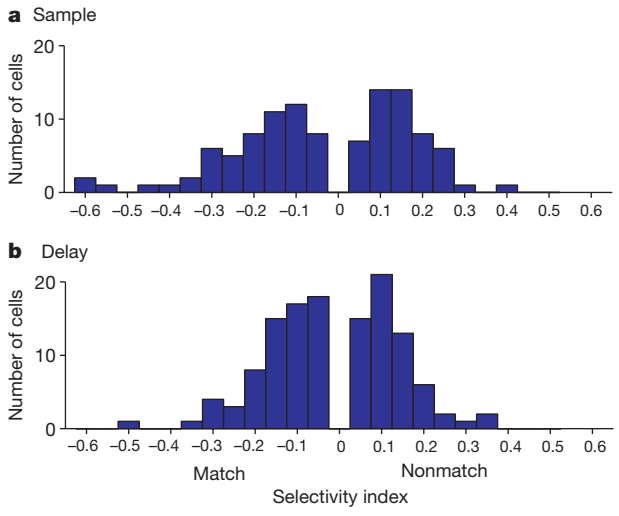

Figure 3 Distribution of the magnitude of rule effect. **a**, **b**, Data from neurons that were rule-selective during the sample epoch (107 neurons; **a**) and delay (127 neurons; **b**). Match and nonmatch refer to the values for neurons exhibiting stronger activity to the match or nonmatch rule.

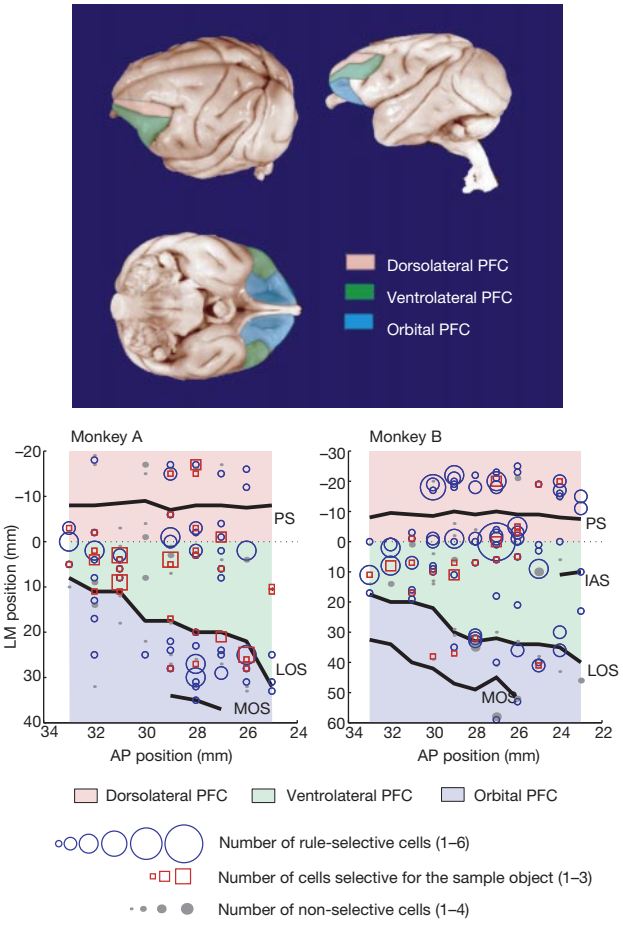

Figure 4 Location of neurons showing rule or object selectivity in either the delay or sample. The anterior–posterior axis was defined with respect to the interaural line, whereas the lateral–medial axis was defined with respect to the ventral lip of the principal sulcus (shown with the dotted line). Dorsolateral PFC (pink) was the cortex lying dorsal to the ventral lip of the principal sulcus. Ventrolateral PFC (green) was between the ventral lip of the principal sulcus and the depth of the lateral orbital sulcus. Orbitofrontal cortex (blue) was medial to the depth of the lateral orbital sulcus. PS, principal sulcus; IAS, inferior arcuate sulcus; LOS, lateral orbital sulcus; MOS, medial orbital sulcus.

Table 1 Neuronal selectivity in different task periods

	Sample epoch				Delay epoch				Either epoch			
	D	V	O	Total	D	V	O	Total	D	V	O	Total
% of cells selective for												
Cue	19	19	17	19	15	8	6	11	31	24	23	27
Rule	29	16	18	22	29	24	23	26	49	37	32	41
Sample object	7	18	8	11	4	12	4	7	10	23	10	14
Cue × Rule	24	31	21	25	14	17	11	14	33	40	28	34
Rule × Sample object	0	3	0	1	1	1	0	1	1	4	0	2
Cue × Sample object	2	0	1	1	3	1	2	2	4	1	2	2

D, dorsolateral PFC ($n = 197$); V, ventrolateral PFC ($n = 169$); O, orbitofrontal PFC ($n = 126$); total, all three areas combined ($n = 492$).

rule-selective neurons in the dorsolateral than in either the ventrolateral or orbital PFC (57/197 or 29%, 27/169 or 16%, 23/126 or 18%, respectively; see Table 1, $\chi^2 = 9.25$, $P < 0.01$) but by the delay, rule-selectivity was equally prevalent (58/197 or 29%, 40/169 or 24%, 29/126 or 23%, respectively; $\chi^2 = 1.85$, $P > 0.1$). The magnitude of rule-selectivity did not differ between the PFC regions (Kruskal–Wallis, $P > 0.1$). There was no difference in the distribution of neurons preferring the match or the nonmatch rules ($\chi^2 = 0.3$, $P > 0.1$); they were evenly split in each PFC region. In fact, neurons preferring different rules were often recorded from the same electrode. Sample-selective neurons were evident in all three regions, but were more numerous in the ventrolateral PFC during both the sample epoch (ventrolateral, 30/169 or 18%; dorsolateral, 13/197 or 7%; orbital 10/126 or 8%; $\chi^2 = 11.8$, $P < 0.01$) and the delay (20/169 or 12%, 7/197 or 4%, 5/126 or 4% respectively, $\chi^2 = 10.3$, $P < 0.01$).

The capacity for abstraction is an important component of higher cognition; it frees an organism from specific associations and gives it the ability to generalize and develop overarching concepts and principles. The ability of PFC neurons to group cues into behavioural categories that are dependent on abstract rules is consistent with observations of a loss of flexibility after PFC damage and with the ability of PFC neurons to form perceptual categories[20]. The prevalence of rule activity is not inconsistent with studies showing the role of the lateral PFC in working memory[21–24] or the orbital PFC in processing affective information[12,25,26], but it does suggest that the abstraction of rules and principles may be an important prefrontal function. □

Methods

Behavioural and recording methods

Trials were randomized and balanced across all relevant features (cues, samples, rules and so on). Monkeys completed about 1,000 trials per day at a consistent level of performance. Eye position remained within 1.7 degrees of the fixation spot throughout the trial and was monitored with an infrared system (ISCAN). Breaks in fixation were not counted in the error rates. The pattern of microsaccades (small eye movements) was similar for different rules. Recordings were made from the PFC of two adult rhesus monkeys (*Macaca mulatta*) using arrays of eight tungsten microelectrodes (FHC Instruments) using a grid (Crist Instruments) with 1-mm spacing. Recordings were localized using magnetic resonance imaging and neurons were randomly sampled; no attempt was made to select neurons on the basis of responsiveness. neural waveforms were digitized and analysed offline using principal components (Plexon Systems).

Four new objects were chosen each day and used throughout a recording session. Use of four samples meant that the identity of the nonmatching test object could not be predicted and thus monkeys needed to remember the current sample and rule. The rule was signified by a brief (100 ms) cue coincident with sample onset (for monkey A, a drop of juice or a blue background indicated the match rule, whereas no juice or a green background indicated the nonmatch rule; for monkey B, juice or a low tone indicated the match rule, whereas no juice or a high tone indicated the nonmatch rule). The sound of the juice delivery solenoid was masked by white noise. Both monkeys performed somewhat better (about 9%) for the juice cues but reaction times did not differ among cues. There was no bias toward responding to the first or second test object (error rates were similar), but monkeys responded about an average of 35 ms faster to the second test, presumably because the response was predictable.

Data analysis

Only data from correct trials were used. Sample activity was summed from 200 ms after sample onset to its offset 600 ms later. Delay activity was summed over the entire delay epoch. All analyses used data from only the sample and first delay epochs although neural activity during the second delay was similar to that seen during the first. The three-way ANOVA was a standard, non-nested, linear model with two levels of interactions and was evaluated at $P < 0.01$. Factors included cue modality (juice versus background colour for monkey A; juice versus tones for monkey B), rule (match versus nonmatch) and the sample object. Rule-selective neurons showed a main effect of rule and no interaction with cue or sample. Likewise, cue or sample-selective neurons showed main effects and no interactions. Magnitude of selectivity was calculated using a standard index (activity to nonmatch minus match rule divided by their sum) and converted to a percentage difference.

Received 20 February; accepted 9 May 2001.

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Acknowledgements

We thank W. Asaad, D. Freedman, C. Kiddoo, M. Warden and M. Wicherski for valuable comments. This work was supported by a NINDS grant, a NIMH Conti Center grant, the RIKEN-MIT Neuroscience Research Center and the Class of 1956 Chair (E.K.M.). J.D.W. was supported by the Wellcome Trust.

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