Modulation of prefrontal cortex activity by information toward a decision rule

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We used fMRI to investigate how the information content of a stimulus influences activity in brain systems that support decision making. Subjects learned decision rules that were based upon the color, shape, or fill pattern of a series of stimuli. Each stimulus was classified by its information content, defined formally by the decision rules it excluded. While activity in dorsolateral prefrontal cortex (dlPFC) increased with increasing stimulus information, activity in the striatum did not. In contrast, within both the striatum and dlPFC, stimuli consistent with the rule evoked greater activity than stimuli inconsistent with the rule. This dissociation indicates that dlPFC supports modification of sets of stimulus-response contingencies while the striatum supports stimulus-specific learning. *NeuroReport* 15:1883–1886 © 2004 Lippincott Williams & Wilkins.

Key words: Basal ganglia; Decision making; Executive function; fMRI; Information; Learning; Prefrontal cortex

INTRODUCTION

To control behavior flexibly, organisms create and alter decision rules based upon sensory experience. One common form of decision making is classification, or partitioning a set of stimuli into distinct response categories [1,2]. The success of classification rests on the information available to the decider. For example, if one knows nothing about the provenance of two paintings, it may be difficult to guess which was created by Michelangelo and which by Titian. Some additional facts, such as that one was painted by an Italian master, provide no new information. However, learning that one was painted in Florence and the other in Venice might lead to an informed decision. In a formal sense, the information provided by a stimulus is defined by the proportion of uncertainty it reduces, where each bit of information reflects the halving of uncertainty.

To investigate the neural systems sensitive to decision information, we measured changes in brain activity using fMRI while subjects performed a novel classification task (Fig. 1). The classification rule changed infrequently, as in paradigms like the Wisconsin Card Sorting Task (WCST) [3], and subjects were required to recognize the active rule as rapidly as possible. However, unlike in the WCST and similar paradigms, subjects responded only to infrequent probe stimuli so that we could control the amount of information provided by each stimulus.

Based on previous studies, we identified two brain regions as likely candidates for information sensitivity. The first was dorsolateral prefrontal cortex (dlPFC), which supports response selection, working memory, and other processes related to the development and modification of behavioral rules [4]. Neuropsychological studies of explicit rule-learning tasks, including the WCST, have shown that patients with dlPFC damage have difficulty learning decision rules [5,6]. Likewise, single-unit studies have shown that dlPFC neurons exhibit rule selectivity [7].

A second candidate system includes striatal regions, which have been postulated to support the learning of categorical relations between stimuli and adaptive behavior [8–10]. The striatum receives significant afferent projections from midbrain dopaminergic neurons, whose activity codes for the difference between expected and observed outcomes [11]. Deficits in striatal function, as found in patients with Parkinson's disease, impair the use of complex decision rules [12]. Although the striatum and dlPFC are highly interconnected and are frequently coactive, recent neuroimaging data suggest a possible distinction: the striatum modifies representations of specific objects while dlPFC modifies abstract task rules [13]. Thus, investigating the sensitivity of these regions to stimulus information is of considerable importance for theories of executive function.

MATERIALS AND METHODS

Subjects: Eight adult subjects (five females, three males; mean age 23 years) participated. None reported any prior neurological condition. All had <1 voxel maximum head motion and had acceptable behavioral performance (see below). Data from an additional five subjects were excluded prior to analysis due to unacceptable head motion or inability to perform the experimental task. All subjects provided written informed consent, and the experiment was approved by the Institutional Review Board of Duke University.

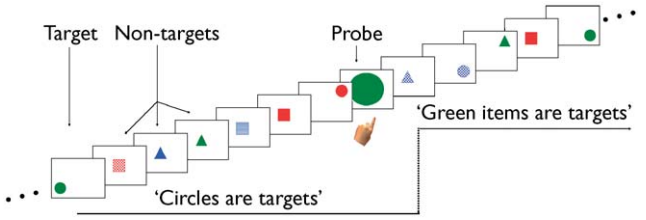

Fig. 1. Design of the experiment. Subjects performed a rule learning task while being scanned using fMRI. Stimuli were simple shapes presented one at a time for 1500 ms with a 1000 ms interstimulus interval. The stimuli could vary in shape, color, or pattern. The subjects' task was to learn a rule that separated targets presented in the periphery from non-targets presented at fixation. For example, if a subject first saw a solid green circle that was a target, the subject could narrow down the active rule to three possibilities (e.g. solid, green, or circle). No additional information would be provided by a subsequent non-target dotted red square, but a solid blue triangle non-target would eliminate one possible rule, leaving green and circle. If a solid green triangle non-target was then presented, it would eliminate one more rule, leaving only circles are targets. We coded the information each stimulus provided by counting how many rules it excluded. The subjects indicated their knowledge of the active rule by responding to infrequent probes. The rules changed periodically and without warning; subjects inferred these rule transitions by noting stimuli whose position violated the previous rule.

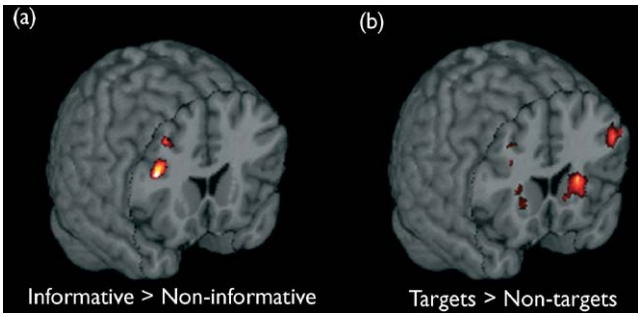

Fig. 2. Dissociation between striatal and dorsolateral prefrontal cortex activity to informative events. (**a**) We identified brain regions whose activity increased proportionally to the amount of information conveyed by each stimulus. Effects significant by random-effects analysis are shown using a red-to-yellow color map ($p < 0.001$ to $p < 0.0001$). Effects of information content were observed in dorsolateral prefrontal cortex, but not in the striatum. (**b**) We also identified voxels that exhibited significantly greater activity to stimuli consistent with the active rule (targets) than to stimuli inconsistent with the active rule (non-targets). Significant target-related activity was observed in both the dorsal striatum and the dorsolateral prefrontal cortex.

Stimuli and experimental design: Subjects learned classification rules and responded to infrequent probe stimuli that tested those rules (Fig. 1). A fixed set of 27 stimuli was created from the combination of three shapes (circle, square, or triangle), colors (red, green, or blue), and patterns (solid, striped, or dotted). Each classification rule was based on one feature (e.g. red stimuli). The task was presented using CIGAL [14].

In the scanner, subjects viewed the stimuli using LCD goggles (Resonance Technologies); each stimulus subtended about 4°, and the total field of view was about $20 \times 16°$. Stimuli were presented in a pseudo-random sequence (duration 1500 ms; interstimulus interval 1000 ms). The position of each stimulus indicated whether it was consistent with the rule. Stimuli that were consistent with the rule, or 'targets', were presented in one of the four corners of the display. Stimuli that were inconsistent with the rule, or 'non-targets', were presented in the center of the display. Each rule was active for 18–22 stimuli before a new rule was chosen randomly. There was no explicit indication of the rule transitions; they were inferred by subjects when stimuli violated the previous rule. Within each rule block, 25% of stimuli were targets and 75% were non-targets.

Subjects did not respond to any of the targets or non-targets, nor did they respond at rule transitions. Instead, they only responded to infrequent (10% of total) and randomly presented 'probes'. The probes were much larger than the other stimuli (9° visual angle) and were thus visually distinct. When a probe was presented, the subject pressed one of two buttons to signal whether it was consistent or inconsistent with the active rule (50% were consistent, 50% were inconsistent).

Subjects first practiced the task for 30 min outside of the scanner. During the fMRI session, subjects participated in 6–9 experimental runs (mean 7.5), each lasting 8 min. On average, subjects viewed about 1440 stimuli and 75 rule changes.

Imaging parameters: fMRI scans were acquired on a 4.0 T GE Signa NVi scanner using a spiral gradient-echo sequence sensitive to blood-oxygenation-level dependent (BOLD) contrast. Each volume consisted of 28 slices parallel to the axial plane containing the anterior and posterior commissures (TR 1250 ms; TE 35 ms; voxel size $3.75 \times 3.75 \times 3.8$ mm), and 380 volumes were collected in each run. To aid in normalization of the functional images, high-resolution T1-weighted SPGR images were acquired at the same orientation (voxel size: $0.9375 \times 0.9375 \times 1.9$ mm).

fMRI data analysis: Initial preprocessing used SPM (Wellcome Department of Cognitive Neurology) to correct for time of slice acquisition, to minimize head motion, to normalize into a stereotaxic space (Montreal Neurological Institute), and to smooth using a Gaussian kernel (8 mm FWHM). Quadratic detrending used custom MATLAB (Mathworks) scripts.

We created separate design matrices for the stimuli and for the information they carried. The stimulus design matrix had four model factors: targets, non-targets, probes, and rule transitions. Stimulus contrasts of interest included targets *vs* non-targets, probes *vs* baseline, and rule transitions *vs* baseline.

For the information design matrix, we coded each stimulus by how many rules it could exclude. For example, if an optimal decision maker knew that the rule was red stimuli, a red target or a green non-target would exclude 0 rules. However, if an optimal decision maker had narrowed down the possible rules to red stimuli or blue stimuli, a red target would exclude 1 rule. Because most stimuli provided relatively little information, we used five model factors: exclusion of 0 rules, 1 rule, 2 rules, 3 rules, and 4 or more rules, each weighted by the number of rules excluded (e.g. stimuli that excluded more rules were hypothesized to have a larger BOLD effect). Our contrast of interest was informative stimuli *vs* non-informative stimuli. To eliminate a potential confound, we excluded all rule transition events from this second design matrix.

Table 1. Clusters of significant positive activity. All regions indicated in this table had more than 6 contiguous suprathreshold voxels ($t > 4.5$). For regions active bilaterally, the coordinates of the highest *t*-value are indicated.

		MNI centroid				
	Laterality	x	y	z	Max *t*	# Voxels
Information increase						
Middle frontal gyrus	R > L	42	18	25	9.2	24/81
Intraparietal sulcus	R	39	−67	32	7.7	9
Targets > non-targets						
Calcarine sulcus	B	0	−84	0	10.5	358
Dorsal striatum	L > R	−21	21	7	7.6	99/18
Inferior frontal sulcus	L	−56	14	35	7.2	26
Middle frontal gyrus	L	−49	4	42	7.0	23
Lateral occipital gyrus	R	39	−67	14	6.6	34
Supramarginal gyrus	L > R	−35	−49	42	6.2	33/24
Intraparietal sulcus	R > L	28	−81	32	6.2	94/158
Lateral occipital gyrus	R	53	−60	−11	6.1	33
Inferior frontal sulcus	L	−49	32	18	5.2	16
Superior frontal sulcus	R	32	4	49	5.2	24
Rule transitions > baseline						
Precentral gyrus	L	−32	−4	53	11.2	47
Lateral occipital gyrus	R > L	35	−77	11	7.4	21/33
Medial frontal gyrus	L	−4	35	46	6.4	8
Middle frontal gyrus	R	42	11	35	5.9	22
Postcentral gyrus	L	−42	−39	49	5.9	12
Superior frontal sulcus	R	32	7	53	5.8	48
Middle frontal gyrus	R	49	25	39	5.2	7
Probes > baseline						
Middle frontal gyrus	R > L	39	25	25	14.7	9/55
Putamen	L	−25	14	7	6.7	10
Medial frontal gyrus	L	−11	14	60	6.6	8
Cingulate gyrus	R	14	18	39	5.2	9

Each contrast was subjected to a second-level random-effects analysis across subjects. Clusters with more than 6 contiguous active voxels ($\alpha < 0.001$) are reported in Table 1.

RESULTS

Behavioral data: Because the probe stimuli could occur at any time during the experimental runs (e.g. before sufficient information to specify a new rule), not even an optimal decision maker could respond correctly to all probe trials. For this reason, we calculated d' measures for all subjects to assess discrimination performance independently of any response biases. For the subjects included in the sample, mean d' was 1.76 (range 0.85–2.70), indicating that they were able to learn the decision rules effectively.

Responses from one button were not recorded for two subjects due to a technical problem. However, both subjects had high hit rates (0.83 and 0.90) and neither subject had any false alarms. Therefore, we conclude that they were performing the task at a near-optimal level, consistent with the other subjects.

fMRI data: Regions exhibiting significant positive activity in our experimental analyses are indicated in Table 1. Our primary analysis identified regions whose activity increased with increasing information provided by a stimulus. We found significant positive effects of stimulus information in the posterior dlPFC, bilaterally, and in the right intraparietal sulcus (Fig. 2a). Significant negative effects were observed in the medial frontal lobe and in the posterior insula.

Significantly greater activity to targets than non-targets was found in the dorsal striatum (both putamen and caudate; Fig. 2b) and the posterior dlPFC, as well as in occipital and superior frontal cortices. Increased activity to rule transitions was observed in posterior dlPFC and the superior frontal lobe, as well as in the occipitoparietal cortex. Note that rule transitions were never explicitly indicated to the subjects, and thus this activity must reflect the subjects' inferences that a rule has changed. Finally, we found significant activity associated with the response probes in dlPFC, the striatum (restricted to the putamen), the medial frontal gyrus, and the cingulate gyrus.

DISCUSSION

Our experimental task was designed to deconfound the effects of the information content of stimuli from the effects of their perceptual and response requirements. We found strong evidence that activity within dlPFC is modulated by the information content of stimuli, both to stimuli that resolve uncertainty about behavioral rules (e.g. increased information) and to stimuli that generate such uncertainty (e.g. rule transitions). Within dlPFC, targets also evoked greater activity than non-targets; the former were typically more informative. Common across these experimental conditions is the requirement to modify a set of stimulus-response contingencies based upon moment-to-moment information from the sensory environment [15].

In contrast, we found significant striatal activity only for the comparison of targets and non-targets, which differed in two ways beside informativeness. First, the targets were

spatially distinct from the non-targets, and thus subjects covertly shifted attention or moved their eyes to fixate the targets. While these shifts may account for the observed activity in superior frontal and occipital cortices, they are unlikely to cause the striatal activity. Recent studies of caudate activity in visual discrimination tasks have indicated that it supports the reward-based control of attention, not eye movements or attentional shifts themselves [16]. Second, the targets provided confirmatory evidence about the rule, while the non-targets provided disconfirmatory evidence. In a wide variety of reasoning tasks, confirmatory evidence is weighted more heavily than disconfirmatory evidence, reflecting the tendency for hypothesis formation and testing [1]. Thus, we interpret the striatal activity in this task to be restricted to stimulus-specific learning that is distinct from the development of explicit behavioral rules mediated by PFC [10,13].

Although our results clearly demonstrated an effect of stimulus information upon dlPFC activity, they raised additional issues. First, while previous studies have implicated the anterior dlPFC (BA 46) in behavioral selection, we observed effects of stimulus information within posterior dlPFC (BA 9). This area of activity was inferior to the postulated location of the frontal eye fields and was anterior to premotor cortex, so we do not believe it reflects attention, eye movements, or motor preparation. Rule learning tasks with more-explicit selection requirements will be necessary to directly compare anterior and posterior dlPFC functions. Of additional note were the superior frontal lobe activity to rule transitions, which may reflect the control of eye movements by the frontal eye fields [17], and the peri-calcarine activity to targets, which may result from increased visual processing of the targets compared with the less-relevant non-targets.

A second issue resulted from the nature of our rule learning task, which did not require responses for each stimulus. Therefore, we could not know the learning strategies used by subjects or the exact information provided by stimuli. Given our subjects' creditable performance, the observed significant activity is likely to reflect true contributions of stimulus information. It remains possible, however, that an improved model would have revealed activity in additional regions. One avenue for future investigations is hypothesis-testing behavior; i.e. that subjects form expectations about possible decision rules and seek evidence to confirm or reject those expectations. Early cognitive psychological studies indicated hypothesis testing is used during rule learning in order to reduce task complexity [1]. Therefore, additional behavioral evidence about subjects' strategies would allow further generalization of neuroimaging results.

Nevertheless, the very measurement of subjects' knowledge of a decision rule evokes activity in regions that support behavioral control, since subjects must select the appropriate response to the probe stimulus. Thus, converging evidence from explicit and implicit decision tasks will be necessary to identify the brain systems associated with the learning and execution of rules for behavior.

CONCLUSION

Using a novel rule learning task, we found that activity within dlPFC was modulated by the amount of information provided by an individual stimulus. Stimuli that reduced uncertainty about the decision rule, or that signaled a change from one rule to the next, evoked significant dlPFC activity. In contrast, activity within the dorsal striatum was greater to stimuli consistent with the decision rule than to stimuli inconsistent with the decision rule. These results emphasize the dynamic nature of prefrontal and striatal contributions to executive control of behavior, with the former supporting the explicit modification of sets of stimulus-response contingencies and the latter supporting implicit stimulus-specific learning.

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