Distinct Portions of Anterior Cingulate Cortex and Medial Prefrontal Cortex Are Activated by Reward Processing in Separable Phases of Decision-Making Cognition

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Background: *Choosing between actions associated with uncertain rewards and punishments is mediated by neural circuitry encompassing the orbitofrontal cortex, anterior cingulate cortex (ACC), and striatum; however, the precise conditions under which these different components are activated during decision-making cognition remain uncertain.*

Methods: *Fourteen healthy volunteers completed an event-based functional magnetic resonance imaging protocol to investigate blood-oxygenation-level-dependent (BOLD) responses during independently modeled phases of choice cognition. In the "decision phase," participants decided which of two simultaneous visually presented gambles they wished to play for monetary reward. The gambles differed in their magnitude of gains, magnitude of losses, and the probabilities with which these outcomes were delivered. In the "outcome phase," the result of each choice was indicated on the visual display.*

Results: *In the decision phase, choices involving large gains were associated with increased BOLD responses in the pregenual ACC, paracingulate, and right posterior orbitolateral cortex compared with choices involving small gains. In the outcome phase, good outcomes were associated with increased BOLD responses in the posterior orbitomedial cortex, subcallosal ACC, and ventral striatum compared with negative outcomes. There was only limited overlap between reward-related activity in ACC and orbitofrontal cortex during the decision and outcome phases.*

Conclusions: *Neural activity within the medial and lateral orbitofrontal cortex, pregenual ACC, and striatum mediate distinct representations of reward-related information that are deployed at different stages during a decision-making episode.*

Key Words: Decision making, anterior cingulate, orbitofrontal, emotion, reward, functional magnetic resonance imaging

Much real-life decision making involves choosing between competing actions associated with uncertain benefits and penalties. Building on demonstrations of impairments in such decision making in samples of neurologic and psychiatric patients (Bechara et al 1996, 1998; Rogers et al 1999a), brain-imaging studies with healthy human volunteers have confirmed the involvement of corticolimbic circuitry in this cognitive function. This circuitry encompasses medial and lateral orbitofrontal cortex (Critchley et al 2000; Ernst et al 2002; O'Doherty et al 2001a, 2003; Paulus et al 2001; Patterson et al 2002; Rogers et al 1999b), anterior cingulate cortex (ACC; Bush et al 2002), striatum (Elliott et al 1999), and amygdala (Thut et al 1997). These findings complement those of other brain imaging studies demonstrating comparable patterns of activity while participants process cues that predict the imminent delivery of reward or punishment (Delgado et al 2000; Elliott et al 2000; Knutson et al 2001a, 2001b; Ramnani and Miall 2003) or process primary and secondary reinforcers (Breiter et al 1997, 2001; Francis et al 1999; O'Doherty et al 2001b; Berns et al 2001).

The involvement of reinforcement circuitry in human choice reflects the fact that deciding between actions associated with uncertain gains or losses is typically an emotive as well as cognitive activity (Damasio 1994). Adaptive decision making must involve weighing the positive and negative consequences of one candidate action against the consequences of other candidate actions in the light of the relative probabilities of good and bad outcomes. Therefore, decision making depends critically on neural and neurochemical systems that process—and integrate for action selection processes—reinforcement information (Rogers et al 2003). In this article, we report an investigation of dissociable roles of distinct sectors of ACC and medial prefrontal cortex (mPFC) in representing reward in independently modeled phases of decision making.

The medial surface of the human frontal lobes is highly differentiated in terms of cell structure and patterns of interconnectivity with other cortical and subcortical systems (Barbas and Pandya 1989; Picard and Strick 1996). In the case of the ACC, anatomical investigations have suggested divisions along several distinct axes (Devinsky et al 1995; Vogt et al 1995) that might reflect separable cognitive and emotional functions (Koski and Paus 2000; Paus et al 1998). One division—between the "cognitive" dorsal ACC (with its marked projections to dorsolateral prefrontal cortex and motor systems) and the "emotional" rostral–ventral ACC (with dense projections to orbitofrontal cortex, striatum, hypothalamus, and brain stem) (Bush et al 2000; Whalen et al 1998)—has been influential in view of evidence for morphologic and functional abnormalities in pregenual and subcallosal ACC in mood and anxiety disorders (Drevets et al 1997). More generally, the rostro–ventral ACC is part of a wider network organized around the ventral mPFC that mediates reinforcement, reward preference, and autonomic functions in contrast to another network organized around the lateral orbital cortex that is characterized by greater innervation from modality-specific sensory areas (Barbas and Pandya 1989; Carmichael and Price 1996; Ongur and Price 2000; Ongur et al 2003).

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Experimental evidence that neural activity in the ACC can represent reward information includes findings that single-unit firing in the ACC relates directly to the imminence of reward in the performance of multi-trial operant schedules (Shidura and Richmond 2002) and that lesions of the ACC impair the acquisition of action–reward associations (Hadland et al 2003) and the calculation of trade-offs between the magnitude of rewards and the physical effort needed to gain access to them (Walton et al 2002). Moreover, the finding that unit-firing in ACC codes changes in reward magnitude associated with current response output (Shima and Tanji 1998) has been replicated by an event-based functional magnetic resonance imaging (fMRI) study (Bush et al 2002), which suggests that the ACC has a particular role in reward-based decision making; however, it remains unclear what part the reward information represented in the ACC plays in different aspects of decision-making cognition. Similarly, although there is abundant evidence that the mPFC represents reward value of primary and secondary reinforcers (Francis et al 1999; Gallagher et al 1999; O'Doherty et al 2001b, 2003; Tremblay and Schultz 1999) and that neural circuitry connecting the mPFC with the ventral striatum supports appetitive and consummatory behaviors (Cardinal et al 2002), relatively little is known about how these representations are deployed when people choose between actions with uncertain outcomes.

In this study, we used an event-based fMRI protocol to investigate changes in the blood-oxygen-level-dependent (BOLD) response within corticolimbic circuitry while participants 1) decided which of two risky gambles they wished to play to maximize monetary reward; and 2) processed the positive or negative outcomes of these choices. The results shed new light on the representation of reward within corticolimbic circuitry in distinct aspects of decision making.

Methods and Materials

Subjects

Fourteen healthy right-handed volunteers (five female, nine male) completed a decision-making task during event-related fMRI. Their mean age was 23.36 ± 1.36 years. The study was approved by the local research ethics committee. All participants gave written, informed consent.

Decision-Making Task

The task used has been described previously (Rogers et al 2003). On each trial, participants were asked to choose between playing one of two simultaneously presented gambles. Each gamble was represented visually by a histogram, the height of which indicated the probability of winning a number of experimenter-defined points (Figure 1). The possible gains were indicated in green text above the histogram, and the possible losses were indicated in red text underneath. One of the gambles (yellow) was a control gamble, consisting of a .5 probability of winning 10 points and a .5 probability of losing 10 points. The alternative "experimental" gamble (blue) varied in the probability of winning, which was either high or low (.66 vs. .33); possible gains, which were either large or small (80 vs. 20 points); and possible losses, which were either large or small (80 vs. 20 points). Orthogonal combination of these three factors produced eight trial types (Table 1). Figure 1 shows the control gamble and an experimental gamble with a .33 chance of winning 80 points (and a .66 chance of losing 20 points).

The control and experimental gambles appeared randomly on the left or right of the display. Participants pressed a button on a response box with the index finger of the right hand to indicate choice of the gamble on the left and another button with the middle finger of the same hand to indicate choice of the gamble on the right. Each display remained on the screen for 4 sec. After the participant's response, a white border illuminated the chosen gamble until the 4-sec display time had elapsed and the visual display was removed. The visual displays subtended approximately 6.98° vertically and 4.18° horizontally.

Figure 1. Example display consisting of a control gamble showing a 50% chance of winning 10 points and a 50% chance of losing 10 points, and an experimental gamble showing a .33 chance of winning 80 points and a .66 chance of losing 20 points.

Visual feedback was given after each choice in the form of a green upward arrow when the participant won the selected gamble ("good outcome"), and a red downward arrow on trials when the participant lost ("bad outcome"). The arrow was displayed for 2 sec. Following this, a revised point score was displayed in white text for 2 sec. The arrows subtended approximately 1.45° vertically and 1.62° horizontally; the points score subtended .34° vertically and 1.03° horizontally.

As previously described (Rogers et al 2003), we included two extra trial types representing choices known to be subject to the nonnormative biases of risk aversion and risk seeking (Kahneman and Tversky 1979). There were no significant imaging results involving these trials in this particular study; these trial types are not discussed further. All 10 trial types were presented (in a pseudorandom order) twice within each block of 20 trials. There were nine blocks of 20 trials. Participants were given a brief sequence of practice trials to acquaint them with the task

Table 1. Eight Types of Experimental Gamble Resulting from the Combination, in a Factorial Design, of Two Levels of Probability, Possible Gains, and Possible Losses

Probability	Possible Gains	Possible Losses
High (.66)	Large (80)	Large (80)
		Small (20)
	Small (20)	Large (80)
		Small (20)
Low (.33)	Large (80)	Large (80)
		Small (20)
	Small (20)	Large (80)
		Small (20)

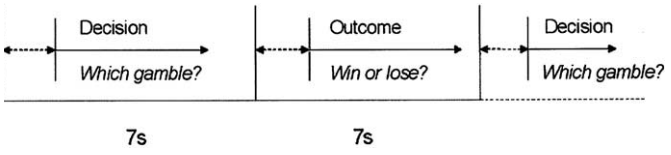

Figure 2. The decision phase and outcome phase of the decision-making trials. Double-headed arrows represent jittering of onset of the gamble displays (in the decision phase) and jittering of the positive or negative reinforcement signals (in the outcome phase) across the range of a repetition time of 2 sec to ensure adequate peristimulus sampling.

procedures and demonstrate that they understood the task displays.

At the beginning of each block, participants were given an "endowment" of 100 points and invited to make choices that would increase this amount by as much as possible. The final point totals accrued by the end of each block were summed to produce a grand total earned over the study. This total was exchangeable for real money at the rate of 1 point = 1 penny. The mean monetary reward earned by the 14 participants was £21.53 ± £1.76.

Event-Related fMRI Trial Structure

Each trial was completed over one single, fixed, 14-sec period, divided into two periods of 7 sec each. During the first 7-sec period (the "decision phase"), the two gambles were displayed for 4 sec. To maximize adequate peristimulus sampling over the hemodymanic response, the presentation of each display was "jittered" randomly over the acquisition time for one scan volume (TR; repeat time) from the start of the 7-sec decision phase (Figure 2).

During the second 7-sec period (the "outcome phase"), the upward or downward arrow indicating whether the participant had won or lost the selected gamble was displayed for 2 sec, followed immediately by the revised point total for another 2 sec. The presentation of the feedback was jittered randomly over the interval of 1 TR from the start of the 7-sec outcome phase.

fMRI Procedures

Echo planar images (EPI) images were acquired on a 3T Varian Inova whole-body scanner (Palo Alto, California), located in the Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB, John Radcliffe Hospital, Oxford, United Kingdom). Participants lay on a padded scanner couch in a dimly illuminated room and wore foam earplugs and headphones. The computer-controlled displays were back-projected onto a screen positioned at the foot of the scanner couch. The participant viewed these displays with the aid of angled mirrors mounted on plastic spectacles. Responses were made on a purpose-built button box.

Measurement of BOLD response within the orbitofrontal cortex is affected by magnetization artifacts (Ojemann et al 1997). We addressed this problem in four ways. First, we used an automated shim procedure that differentially weights the homogeneity of the shim to a localized region of interest drawn around the inferior frontal lobes. This procedure has been shown to significantly reduce signal dropout and geometric distortion within a specified region of interest (Wilson et al 2002). We were able to quantify the extent to which the geometric distortion was improved by measurement of the magnetic field homogeneity before and after the local shimming was applied (because the pixel shift in an EPI data set is directly proportional to the B_0 error). In the current study, calculations based on separate B_0 maps acquired after global and local shims for nine of the 14 participants revealed 20%–30% reductions in pixel-shift mislocations after the local shim. Second, we acquired data in coronal slices so that the through-plane direction was perpendicular to the direction of the main susceptibility gradients, thus resulting in minimal through-plane dephasing. Third, slice thickness was reduced to 5 mm (with in-plane resolution of 3 mm) so that intravoxel dephasing was reduced. Finally, we used a short echo time (TE) of 27 msec to minimize phase dispersion at the time of the echo. The matrix was 64^2; the field of view was 192 mm × 192 mm, and the flip angle was 90°. With adoption of these parameters, the fMRI protocol was restricted to 16 T2*-weighted images covering the anterior pole back to the vertical plane at the anterior commissure (VCA). A 64-slice anatomical T1-weighted data set was acquired with a slice thickness of 3 mm for coregistration with the EPI data.

Statistical Analysis (Behavioral Measures)

The behavioral data were analyzed with SPSS 11.0 (SPSS Inc., Chicago, Illinois). The principle measure was the proportion of trials on which participants chose the experimental over the control gamble ("proportionate choices"). The proportionate choice was arcsine-transformed, as is appropriate whenever variance is proportional to the mean (Howell 1987); however, all data reported in the text, figures and tables describe untransformed values. The proportionate choice and mean deliberation time (msec) were analyzed with repeated-measures analysis of variance with the between-subject factor of gender and within-subject factors of probability (high vs. low), possible gains (large vs. small), and possible losses (large vs. small).

Statistical Analysis (fMRI)

Analysis was carried out with FEAT (FMRI Expert Analysis Tool) version 5.00, part of FMRIB's software library (see www.fmrib.ox.ac.uk/fsl). First-level (single-subject) general-linear model results were estimated (Woolrich et al 2001) and transformed, after spatial normalization, into standard (MNI152) space (Jenkinson et al 2002). For the decision phase of the trials, we modeled the presentation of the gamble displays listed in Table 1 as independent events of 4-sec duration. For the outcome phase, we modeled good outcomes as one event consisting of the upward arrow displayed for 2 sec and the subsequent increased point score displayed for 2 sec. We modeled bad outcomes as another event consisting of the downward arrow displayed for 2 sec and the subsequent decreased point score displayed for 2 sec. Higher-level analysis was carried out with FLAME (FMRIB's Local Analysis of Mixed Effects; Woolrich et al, in press). Z (Gaussianized T/F) statistic images were thresholded with $Z > 2.3$ and a (corrected) cluster significance threshold of $p = .05$ (Friston et al 1994; Forman et al 1995; Worsley et al 1992).

Results

Behavioral Measures

Consistent with previously published results (Rogers et al 2003), participants chose the experimental gamble significantly more often when its probability of winning was high compared with when its probability of winning was low [$F(1,12) = 17.08$, $p < .0001$] (see Figure 3A), significantly less often when its possible losses were large compared with when its possible losses were small [$F(1,12) = 33.37$, $p < .0001$] (Figure 3B), and significantly more often when its possible gains were large compared with when they were small [$F(1,12) = 33.37$, $p < .0001$] (Figure 3C). There was no significant difference between proportionate

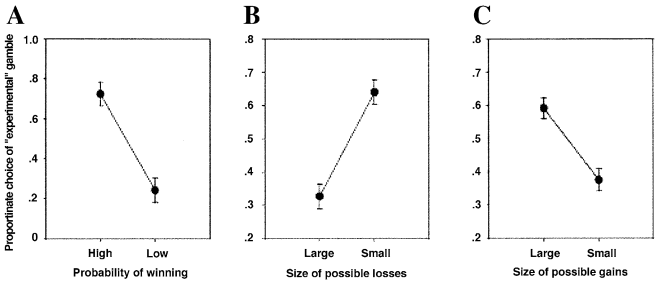

Figure 3. Proportionate choice of the experimental gamble over the control gamble for 14 participants as a function of variation of three factors. (**A**) High versus low probability of winning; (**B**) large versus small possible losses; (**C**) large versus small possible gains.

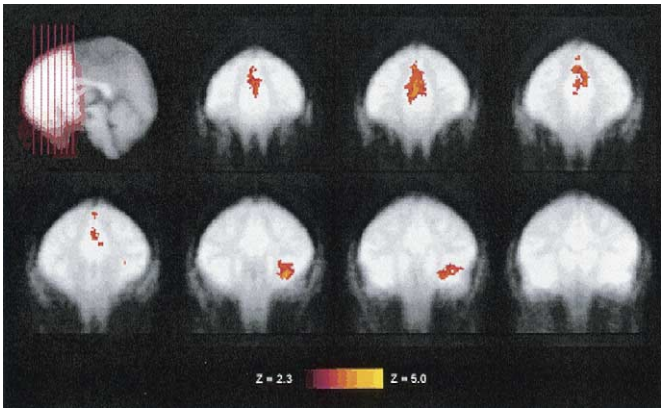

Figure 4. Decision phase: increases in blood-oxygenated-level-dependent response during decisions between gambles in which the experimental gamble was associated with large gains compared with small gains. Signal is rendered on echo planar images (seven coronal sections) averaged over 14 participants after transformation into standard space.

choice of the experimental gamble for men and women (.51 ± .04 vs. .47 ± .03), or any interactions involving gender, the probability of winning, and the size of possible gains or losses.

Participants made slightly faster choices when the experimental gamble was associated with a high probability of winning compared with a low probability of winning (1970 ± 179 msec vs. 2042 ± 179 msec); however, this effect was not significant [$F(1,12) = 2.70$, $p = .13$]. By contrast, participants made significantly slower choices when the experimental gamble was associated with large compared with small losses (2040 ± 164 msec vs. 1971 ± 191 msec) [$F(1,12) = 4.64$, $p = .05$]. There was no significant difference between times needed to make choices when the experimental gamble was associated with large possible gains compared with small gains (2035 ± 183 msec vs. 1976 ± 173 msec) [$F(1,12) = 1.12$, $p = .31$] or between times needed to make decisions for male compared with female participants (1798 ± 203 msec vs. 2161 ± 266 msec) ($F < 1.00$).

BOLD (Decision Phase)

Comparison of the BOLD response during the decision phase of those trials in which the possible gains associated with the experimental gamble were high compared with when they were low revealed two sets of significant peaks (Table 2).

One set of peaks was located along the medial wall of the frontal lobes and extended in a dorsal direction from the supracallosal anterior cingulate cortex, just anterior to the genu, through the paracingulate region and along the superior frontal gyrus (Figure 4). This activity seems to be bilateral but was greater on the left than on the right. The other set of peaks was less extensive but was maximal in the right posterior ventrolateral PFC.

By contrast, comparison of the BOLD response during the decision phase of trials in which the probability of winning on the experimental gamble was high with trials in which the probability of winning was low, and comparison of trials in which the possible losses were large with those in which they were small did not show significant signal changes.

BOLD Measures (Outcome Phase)

Investigation of BOLD responses during the outcome phase of trials in which participants won their chosen gamble (good outcomes) compared with trials on which they lost (bad outcomes) revealed two sets of significant peaks (Table 3). The first was distributed within the posterior orbitomedial surface of the left frontal lobes and extended in a posterior direction to incorporate the ventral striatum bilaterally (Figure 5). Good outcomes were also associated with activation in the ventral mPFC bilaterally. The second set of peaks associated with good outcomes compared with bad outcomes was located along the

Table 2. Decision Phase: Significant Increases (Local Maxima) in BOLD Response Associated with Deliberating over Choices in Which the Experimental Gamble Was Associated with Large Gains Compared with Small Gains

Localization	Cluster Size (voxels)	*p*	Max *Z*	x (mm)	y (mm)	z (mm)
Anterior Cingulate Cortex (ventral BA 24)			3.63	−2	42	8
Paracingulate Sulcus (BA 32)			3.32	−0	44	36
Anterior Cingulate Cortex			3.50	2	44	12
Anterior Cingulate Cortex			3.62	2	46	16
Anterior Cingulate Cortex	**941**	**.000442**	**3.83**	**2**	**46**	**20**
Anterior Cingulate Cortex			3.55	6	46	20
Frontal Operculum/Orbitofrontal Cortex	**391**	**.048900**	**4.08**	**36**	**24**	**−12**
Frontal Operculum/Orbitofrontal Cortex			3.57	40	22	−12
Frontal Operculum/Orbitofrontal Cortex			3.45	32	22	−14
Frontal Operculum/Orbitofrontal Cortex			3.03	46	22	−6
Frontal Operculum/Orbitofrontal Cortex			2.98	50	22	−4
Frontal Operculum/Orbitofrontal Cortex			3.15	36	28	−2

Bold values signify global maximum of peak.
BOLD, blood-oxygen-level-dependent; BA, Brodmann's area; Max, maximum.

Table 3. Output Phase: Significant Increases (Local Maxima) in BOLD Response Associated with Those Trials for Which Participants Won Their Chosen Gamble (Good Outcomes) Compared with Trials for Which They Lost (Bad Outcomes)

Localization	Cluster Size (voxels)	*p*	Max *Z*	x (mm)	y (mm)	z (mm)
Posterior Orbitofrontal Cortex	**5205**	**4.04e-16**	**5.89**	**−10**	**16**	**−18**
Posterior Orbitofrontal Cortex			5.55	−12	10	−16
Posterior Orbitofrontal Cortex			5.35	−14	14	−16
Posterior Orbitofrontal Cortex			5.76	20	12	−18
Posterior Orbitofrontal Cortex			5.11	22	20	−10
Anterior Cingulate Cortex			4.86	12	20	−10
Superior Frontal Sulcus	**888**	**.000165**	**4.05**	**−22**	**24**	**54**
Middle Frontal Gyrus (BA 46)			3.59	−22	30	50
Superior Frontal Sulcus			3.64	−18	26	50
Superior Frontal Sulcus			4.04	−28	32	44
Superior Frontal Sulcus			3.67	−26	30	44
Superior Frontal Sulcus			3.64	−26	26	38

Bold values signify global maximum of peak.
BOLD, blood-oxygen-level-dependent; BA, Brodmann's area; Max, maximum.

middle frontal gyrus (Brodmann's area 46) and the superior frontal sulcus on the left but not the right.

Rendering significant peaks from the decision and outcome phases onto the mean structural brain for all 14 participants demonstrates the distributions of activations associated with the two phases of the trials (Figure 6). Decisions involving gambles associated with large possible rewards activated pregenual ACC, mPFC and paracingulate regions, and lateral posterior orbitofrontal cortex on the right; good outcomes for chosen gambles were associated with increased activity in ventral mPFC, subcallosal ACC, and ventral striatum.

Overlap between activations associated with the decision phases and the outcome phases was confined to a relatively small region of cortex just anterior of the genu, extending between 6 mm and 20 mm above the anterior commissure in standard MNI152 space.

Discussion

These results demonstrate that neural activity within orbitofrontal cortex, ACC, and striatum mediates distinct representations of reward information that are activated at different stages during a decision-making episode. Specifically, an area encompassing pregenual ACC, dorsal mPFC, and right posterior lateral orbitofrontal cortex showed enhanced activity related to the magnitude of possible gains while participants decided which of two simultaneously presented gambles to play to maximize monetary reward; by contrast, the subcallosal ACC, ventral mPFC, and striatum showed increased activity in response to good outcomes (winning) rather than bad outcomes (losing) while participants processed the consequences of their choices.

Before considering the theoretic implications of our findings, we will consider some methodologic issues. First, we acknowledge that the imaging protocol sets limits on the generalizability of the observed results. The primary targets of our investigation were the inferior frontal lobes and basal forebrain. Imaging these

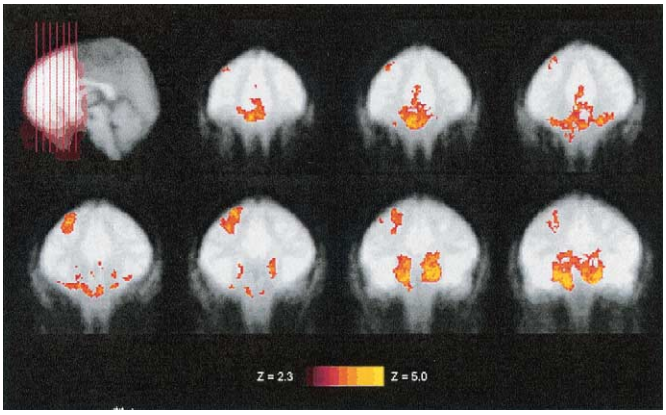

Figure 5. Outcome phase: increases in blood-oxygenated-level-dependent response associated with those trials in which the participants won monetary reward (good outcomes) compared with trials in which they lost reward (bad outcomes). Signal is rendered on echo planar images (seven coronal sections) averaged over 14 participants after transformation into standard space.

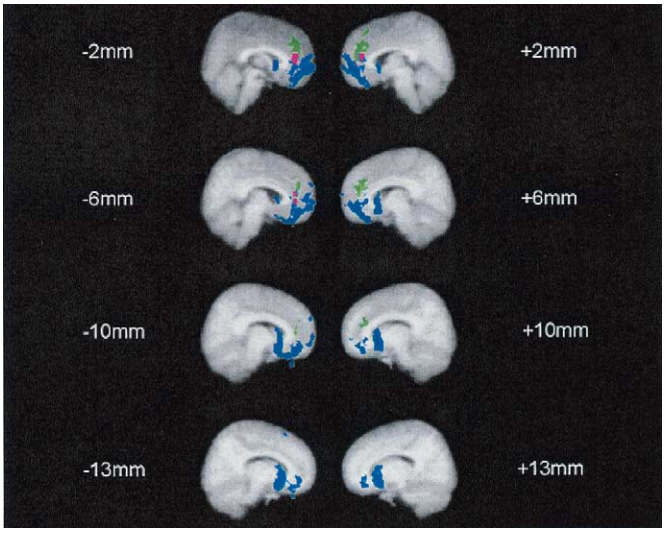

Figure 6. Green areas represent regional increases in blood-oxygenated-level-dependent (BOLD) response during decisions in which the experimental gamble was associated with large compared with small gains; blue areas represent regional increases in BOLD response associated with those trials in which the participants won monetary reward (good outcomes) in the outcome phase compared with trials in which they lost (bad outcomes); pink areas represent overlap of green and blue. Rendered on mean T1-weighted images (for 14 participants) after transformation into standard space.

structures is known to be susceptible to signal loss and geometric distortion, especially at high fields (Ojemann et al 1997). To counter these problems, we used coronal acquisition, reduced slice thickness, and short echo times. We also used an automatic localized shim procedure that reduces signal loss and geometric distortion when imaging the inferior frontal lobes (Wilson et al 2002). Calculations based on separate B_0 maps acquired after global and local shims for a subset of participants revealed 20%–30% reductions in pixel-shift mislocations—equivalently, B_0 error—in the latter case, which suggests that distortion was similarly reduced in our protocol. Nevertheless, our EPI images show clear signs of geometric distortion and, in the absence of fully validated procedures for unwarping this distortion, localization of activations to cortical structure must remain approximate.

The use of coronal acquisition also had the effect of limiting our coverage to a field of view from the frontal pole to just posterior to the VCA plane, leaving open the possibility that there were other changes in the BOLD response relating to our main comparisons that we were not able to visualize. These might have included signal changes in temporal or posterior parietal cortex associated with good or bad outcomes or, perhaps, different strategies of task performance (cf. Knutson et al 2003; Paulus et al 2002); however, in this study, our primary objective was to examine changes in BOLD within mPFC associated with the processing of affective cues while choosing between gambles, and the imaging protocol adopted clearly shows discriminable and significant signal changes within this field of view.

Secondly, it is notable that our results showed changes in BOLD response exclusively in response to processing appetitive cues associated with the gambles and outcomes of participants' choices but not in response to processing other kinds of cues. We did not see BOLD changes during decisions between gambles with high probabilities of winning (in which reward expectancy would have been high) compared with low probabilities of winning (in which reward expectancy would have been low); nor during decisions between gambles with large losses compared with small losses. This probably reflects the format of the gambles as presented to our participants. Human decision makers are known to make different choices depending on whether the alternatives are framed to highlight positive or negative outcomes (Kahneman and Tversky 1979). In the present study, the gambles and experimenter instructions were constructed to emphasize that participants could come to the laboratory and, starting from nothing, win a relatively significant amount of money; in other words, the decisions were framed positively. Therefore, our results should be interpreted as most relevant to what happens when people make choices to maximize available reward. We are conducting studies to examine changes in BOLD when the choice is between negatively framed options.

mPFC and Decision Making under Uncertainty

These findings add to evidence of functional heterogeneity in the human mPFC (Devinsky et al 1995; Koski and Paus 2000; Paus et al 1998; Vogt et al 1995). As noted earlier, the rostral–ventral ACC forms part of an interconnected network organized around the ventral mPFC that projects to a number of cortical and subcortical structures, including the ventral striatum and the amygdala; more generally, this mPFC network encompasses a wide range of neural and neurochemical systems implicated in autonomic and visceral control (Carmichael and Price 1996; Ongur and Price 2000; Ongur et al 2003). In summary, the performance of this task was associated with significant signal changes within a corticolimbic network strongly implicated in reinforcement, emotion, and the control of mood (Drevets el al 1997).

Intriguingly, it seems that a region centered around pregenual ACC but extending upward through paracingulate cortex into the anterior part of the dorsal mPFC has a particular role in representing reward magnitude while decision makers decide between which of two gambles they wish to play. This activity was decisively located within that area of the rostral–ventral ACC, denoted as the "emotional" sector of the ACC and incorporating areas 32, 24a, 24b, 24c, and 25 (Bush et al 2000). This region of the ACC, also incorporating the overlying area in the mPFC, has previously been found to be activated in other brain-imaging studies of emotion (Phan et al 2002; Phillips et al 1998). Several of these have required participants to actively evaluate pictorial stimuli (Lane et al 1997a, 1997b; Taylor et al 2003) or compounds of pictorial and verbal stimuli (Teasdale et al 1999) in explicitly emotional terms, consistent with the hypothesis that these areas play a pivotal role in mediating cognitive operations over emotional material; however, there is disagreement among researchers as to which cognitive operations involving emotional stimuli recruit the mPFC and whether these operations are mediated solely by rostral ACC or the dorsal mPFC (Phan et al 2002). For example, in the context of the current results, it might be that large reward associated with the experimental gamble activated mPFC during the decision phase by increasing emotional arousal (Phan et al 2003) or by redirecting attention to various internal states relevant to task performance (Casteli et al 2000; Gusnard et al 2001), including the behavioral goal of maximizing reinforcement. Further research will be needed to clarify this issue.

On the other hand, we acknowledge that there must be at least some ambiguity in the interpretation of the events used to model BOLD responses during the decision phase of the trials. Specifically, reward-related activations associated with the decision phase (in pregenual ACC, dorsal mPFC, and right lateral orbitofrontal cortex) were modeled in relation to the onset and duration of the gamble displays themselves. The 4-sec duration of these events would have been long enough to include both the cognitive activity required to choose which gamble to play and the production of the appropriate motor response. Although motor response type (left vs. right finger presses) and participant response rate were balanced across all our comparisons, it is possible that at least some of the signal change observed in the decision phase reflects modulation of motor selection and output processes by the prospect of larger magnitudes of reward while deciding between gambles (cf. Bush et al 2002).

In this context, it is relevant to note that the ACC activity associated with processing large reward magnitudes during the decision phase seems to be somewhat anterior to that reported by Bush et al (2002) in their study of ACC activity in reward-related decision making. In that study, the peaks associated with reward processing were located in individual subjects within a more caudal area bounded between $y = 4$ mm and $y = 17$ mm. By contrast, the peaks for individual participants in the present study were located between $y = 36$ mm and $y = 44$. The precise reason for this difference remains unclear; however, it might be that differences in the kind of choices made by the participants, and the cognitive operations invoked, are important. In general, the caudal region of the ACC is thought to support a system that mediates attentional responses to conflicts arising at different levels of information processing but especially in response selection and output (Botnivick et al 2001; van Veen et al 2001). Bush et al (2002) reported their reward-related activity in this

more caudal region in trials in which participants were required to alter successive responses to obtain a maximum amount of reward. Therefore, it is possible that this activity might have arisen through the requirement to alter an active response repertoire to continue to maximize available reinforcement. By contrast, the pregenual ACC peak reported in the present study was associated with deliberating about differing magnitudes of reward in a way completely uncorrelated with any increase in conflict or consequent changes in overall response output. This suggests that the most rostral cingulate system mediates a representation of reward value that is not immediately tied to other aspects of more caudal ACC function (Devinsky et al 1995).

Finally, increased magnitude of gains associated with the experimental gamble was also associated with increased BOLD response within right posterior orbitofrontal cortex. This replicates other studies that have demonstrated similar activations while participants complete a decision-making task (Critchley et al 2000; Elliott et al 1999; Rogers et al 1999b). It is also consistent with emerging evidence that impairments in decision making are greater in neurologic patients who have sustained damage to the right orbitofrontal cortex compared with those who have suffered damage to the left orbitofrontal cortex (Tranel et al 2002). This aspect of our results also qualifies recent claims that reward is coded by medial parts of the orbitofrontal cortex, whereas punishment is coded by lateral parts of the orbitofrontal cortex (O'Doherty et al 2001a, 2003). We find that reward magnitude during the decision phase is associated with a peak within the right posterior lateral orbitofrontal cortex. Because this peak represents the difference in activity associated with deliberating about gambles with high levels of reward and activity associated with deliberating about gambles with low levels of reward, these data suggest that the orbitofrontal cortex provides representations of reward magnitude in lateral as well as medial areas, at least while decision makers deliberate between risky gambles. Interestingly, Elliott et al (2003) report that activity in an adjacent area of right posterior orbitofrontal cortex was enhanced by the delivery of either small or large rewards relative to midrange rewards.

mPFC and the Processing of Signaled Reward

In addition to the putatively "evaluative" role of pregenual ACC and dorsal mPFC in the decisional aspects of risky choice, the present study provides evidence that the mPFC plays a prominent role in processing signaled reinforcement. Specifically, the BOLD response was enhanced when participants processed signals indicating good compared with bad outcomes. This activity incorporated a small region around and beneath pregenual ACC and a larger region, including the inferior frontal gyri and posterior orbitomedial cortices, bilaterally. In general, these data are consistent with several studies that have shown that the delivery of primary reinforcers, such as pleasant taste and touch stimuli (Francis et al 1999; O'Doherty et al 2001b), or secondary reinforcers, indicating the delivery of monetary reward, are associated with activity within the medial orbitofrontal cortex and the striatum (Breiter et al 2001; Delgado et al 2000; Elliott et al 1999; Knutson et al 2001b, 2003; Ramnani and Miall, 2003).

One feature of current research into human reinforcement mechanisms is the use of fMRI methodology to explore the possibility that different portions of corticolimbic circuitry represent different aspects of reward information, with some suggestion that the mPFC registers the delivery of reward versus punishment (Breiter et al 2001; Elliott et al 2003) and/or tracks the magnitude of delivered reinforcement as a function of expectation (Breiter et al 2001; Knutson et al 2003). In the present study, the signal changes observed during the outcome phase of the decision-making trials (subcallosal ACC, ventral mPFC, and striatum) were modeled in relation to the presentation of feedback information that indicated either good or bad outcomes; however, this feedback information was actually the composite of two quite distinct events: an upward or downward arrow displayed for 2 sec (indicating the delivery of reward or punishment), followed by an updated point score displayed for 2 sec (indicating the resulting fluctuations in total reward across trials). Therefore, the extent to which the associated signal change in ventral mPFC was driven by the delivery of reward versus punishment, or by upward or downward fluctuations in already-acquired reward is uncertain.

Notwithstanding this uncertainty, the central finding of the experiment remains unaffected: that deciding between gambles associated with large rewards compared with small rewards modulated different parts of corticolimbic circuitry compared with the processing of good compared with bad outcomes of these choices. Further research will be needed to examine the extent to which these differential patterns of activation are driven by interactions between reward information and motor preparation/output processes or by different kinds of feedback cues indicating the delivery of reward or punishment or relative change in reward.

Finally, the neural activity within the ventral mPFC associated with processing reinforcement signals during the outcome phase of the decision-making trials was coupled with extensive activity within the caudate nucleus and ventral striatum bilaterally. It is likely that this activity encompassed the anterior parts of the nucleus accumbens. Therefore, processing positive reinforcement signals increased neural activity within circuitry known to support learning about secondary reinforcers (Cardinal et al 2002) as well as the activation of response repertoires associated with the presentation of such reinforcers (Mogenson et al 1980). It is also intriguing that the neural structures activated during the decision phase (i.e., pregenual ACC) and outcome phase of the trials (i.e., ventral mPFC and striatum) form a circuitry supporting important classes of appetitive behaviors that depend on the motivational significance of exteroceptive stimuli (Parkinson et al 2000). Further research is needed to discover whether the pattern of activity within this circuitry found in the decision and outcome phases of our decision-making trials reflects learning about which signals within the task displays predict differently valenced outcomes, and/or the activation of conditioned responses that guide decision-making processes to adaptive conclusions (Damasio 1994).

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