Available online at www.sciencedirect.com
SCIENCE DIRECT
Cognitive Brain Research 23 (2005) 61–70
COGNITIVE BRAIN RESEARCH
www.elsevier.com/locate/cogbrainres

Research report

Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making

M.X. Cohen[a,b,*], A.S. Heller[c], C. Ranganath[b,c]

[a]Department of Epileptology, University of Bonn, Germany
[b]Department of Psychology, University of California, Davis, CA 95616, USA
[c]Center for Neuroscience, University of California, Davis, CA 95616, USA

Accepted 8 January 2005
Available online 19 February 2005

Abstract

Recent neuroscience research is beginning to discover the brain regions involved in decision-making under uncertainty, but little is known about whether or how these regions functionally interact with each other. Here, we used event-related functional magnetic resonance imaging to examine both changes in overall activity and changes in functional connectivity during risk-taking. Results showed that choosing high-risk over low-risk decisions was associated with increased activity in both anterior cingulate and orbitofrontal cortices. Connectivity analyses revealed that largely distinct, but somewhat overlapping, cortical and subcortical regions exhibited significant functional connectivity with anterior cingulate and orbitofrontal cortices. Additionally, connectivity with the anterior cingulate in some regions, including the orbitofrontal cortex and nucleus accumbens, was modulated by the decision participants chose. These findings (1) elucidate large networks of brain regions that are functionally connected with both anterior cingulate and orbitofrontal cortices during decision-making and (2) demonstrate that the roles of orbitofrontal and anterior cingulate cortices can be functionally differentiated by examining patterns of connectivity.

Theme: Neural basis of behavior
Topic: Motivation and emotion

Keywords: Decision-making; fMRI; Functional connectivity; Orbitofrontal cortex; Anterior cingulate; Amygdala

1. Introduction

The ability to make decisions under uncertain conditions is arguably one of the most important functions of the brain. Current evidence suggests that ventromedial prefrontal areas including the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are critically involved in the process of evaluating and choosing between decision options when the outcomes of those decisions are unknown or uncertain [5,22,33,40,43]. For example, patients with damage to OFC show marked impairments in learning optimal decision-making strategies to avoid long-term monetary losses [5,6] and are also impaired in adapting decision-making behavior to changes in stimulus–reward contingencies [51,52]. Lesions in ACC also produce impairments in behavioral control and the ability to evaluate risks or effort involved in seeking rewards [12,44,62]. Consistent with these observations, recent neuroimaging studies have demonstrated that regions including OFC and ACC become especially active during decision-making tasks that involve uncertainty or risk [17,24,49]. Activity in these regions increases with increasing potential failure or effort associated with a potentially rewarding action [17,62]. It is thought that OFC maintains stimulus–reward associations [51,52] and that ACC houses mechanisms that help control and select appropriate behaviors [58].

However, regions of the brain do not act in isolation of each other, but rather must work together as a system [33,56].

* Corresponding author. Department of Epileptology, Sigmund-Freud-Str. 25, Bonn 53105, Germany.
E-mail address: mcohen@ucdavis.edu (M.X. Cohen).

0926-6410/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.cogbrainres.2005.01.010

For example, damaging anatomical connections between OFC and amygdala lead to similar impairments in learning and decision-making as those produced by damage to either region alone [29]. Thus, one challenge for understanding the neurobiological mechanisms of decision-making is to elucidate not only the brain regions that exhibit significantly heightened activity during decision-making, but also to understand how different regions of the brain interact on the functional–anatomical level during decision-making. To our knowledge, functional connectivity has not been examined in the context of decision-making, but based on known neuroanatomical connections with OFC and ACC, a number of candidate regions might exhibit functional connectivity during decision-making. For example, both OFC and ACC have extensive bilateral cortical connections with ventral and dorsal prefrontal cortex (PFC), insula, and parietal cortex, as well as with subcortical connections with amygdala, striatum, and thalamus, as well as with each other [11,37,60]. However, although broad anatomical connections within the brain are known, it is not clear whether these anatomical connections are mirrored in functional connections, and further, whether participants' decisions can modulate the strength and nature of these functional connections.

We designed a functional magnetic resonance imaging (fMRI) study that allowed us to experimentally separate neural activity related to choosing between high-risk and low-risk decision options from other processes engaged during decision-making, such as reward anticipation and evaluation. On each trial during the experiment, participants chose one of two uncertain gambles: a high-risk (40% chance of winning $2.50) or a low-risk (80% chance of winning $1.25). This decision was separated in time from learning the outcome of the decision (win or lose), which allowed us to identify regions of the brain specifically engaged when choosing between decision options with uncertain outcomes, and then to further explore patterns of functional connectivity with these task-activated regions.

2. Materials and methods

2.1. Participants

Sixteen participants (aged 20–27, 9 male) volunteered to be in the study in exchange for payment by the hour. Participants were recruited from the graduate and undergraduate population at the University of California, Davis. All participants were screened for contra-indications of performing an MRI experiment (e.g., pace-makers, psychoactive drugs, etc.), and signed informed consent documents prior to the start of the experiment.

2.2. Task design

On each of 167 trials, participants first saw a visual cue (a white circle in the center of a black screen) on the screen that indicated that they needed to choose one of two decision options in attempt to win money: a low-risk decision, for which participants were 80% likely to win $1.25 and 20% likely to receive nothing ($0.00); or a high-risk decision, for which participants were 40% likely to win $2.50 and 60% likely to receive nothing. Participants indicated their decision by pressing one of two buttons on a response box and were encouraged to indicate their decision as quickly as possible. Following the decision, a 7.5 s anticipation period ensued before text appeared on the screen that indicated how much participants had won on that trial. The feedback was followed by a variable, 7–13 s inter-trial-interval (ITI) before the next trial began. This design allowed us to distinguish between activity related to making the decision, anticipating the outcome, and evaluating the outcome on each trial [17,20,31,47,48]. The task was programmed so that, on each trial, the computer generated a random number between 1 and 100. If the participant chose, for example, a high-risk gamble, and the random number was less than 40, the participant won. Thus, not only were the rewards given on a random schedule, the probability of winning on each trial was independent of events that occurred on previous trials. Participants were informed of the probabilities of outcomes associated with each decision option and were trained on this task prior to the start of the experiment for approximately 20 min, or until they stated that they understood the task. This training minimized effects of learning and trial-and-error guessing strategies during the task. In addition to decision trials, 133 no-decision trials were included in which participants simply had to make a behavioral response to get $2.50 (with no decision required). In the present paper, only brain activity related to the decision phase during decision trials are discussed. In total, 8 functional runs were acquired, each run with approximately 38 trials per run, plus an addition run for a visual–motor task to derive a subject-specific hemodynamic response function (see below), which yielded a total experiment time of approximately 2 h (including anatomical scans and brief rest breaks in between scanning runs).

2.3. fMRI acquisition

MRI data were collected on a 1.5 T GE Signa scanner at the UC Davis Research Imaging Center. Functional imaging was done with a gradient echo EPI sequence (TR = 2000, TE = 40, FOV = 220, 64 × 64 matrix, voxel size = 3.475 × 3.475 × 5 mm), with 24 oblique axial slices (tilt angle: ~−15° from ac–pc line). Co-planar and high-resolution T1 weighted images were also acquired from each participant. EPI data were realigned to the first volume, corrected for slice-timing differences, co-registered with the anatomical scan, spatially normalized to the MNI space, resampled to 3.5 mm isotropic voxels, and spatially smoothed with an 8 mm FWHM kernel using SPM99 software (Wellcome Department of Imaging Neuroscience, London, UK).

2.4. Statistical analyses

Event-related blood oxygenation level dependent (BOLD) responses were estimated using multiple regression in Voxbo software (www.voxbo.org). Separate covariates modeled the decision, anticipation, and outcome phases of each type of event, relative to the ITI. All regression models incorporated empirically derived estimates of intrinsic temporal autocorrelation [1] and filters to attenuate frequencies above .25 Hz and below .01 Hz. BOLD responses to each event type were modeled with empirical hemodynamic response functions derived from each participant using BOLD responses in the central sulcus during a visuomotor response task [2,28]. The mean of each scanning run, the global signal (orthogonalized with respect to the design matrix [18]), and an intercept were additionally included as covariates.

Following single-subject analyses, images of parameter estimates for each contrast of interest (e.g., high-risk vs. low-risk decisions) were entered into a one-sample *t* test in which the mean estimate across participants for each voxel was tested against zero, thus treating subject as a random factor. Significant regions of activation were identified using an uncorrected, two-tailed threshold of $P < .001$ and a cluster threshold of 6 contiguous voxels. In the figures, activations are overlaid on a single participant's T1 image, using MRIcro software [53] (convolved with an embossing filter kernel in matlab to produce the observed coloration).

2.5. Connectivity analyses

To examine task-induced patterns of connectivity in our task, we used regression techniques to test for brain areas in which activity during the decision-making phase of the task correlated significantly with activity in an a priori chosen seed region. To do this, we extracted the entire time course of activity in a particular region (e.g., a cluster of voxels in ACC that showed significant activation during the task) for the whole experiment and multiplied that time course with a condition vector that was ones for 6 TRs following the decision cue, and zeros otherwise (see Fig. 1). These resulting vectors were then used as covariates in a separate regression, which included the high and low-risk vectors as the independent variables of interest, as well as the nuisance covariates used in the original regressions, as described above. These independent variables are similar to the bilinear terms ("psychophysiological interaction terms") used in dynamic causal modeling of fMRI data [27], and similar analyses have been used previously to examine functional connectivity [45]. The resulting parameter estimates thus represent the extent to which decision-related activity in each voxel correlates with decision-related activity in the seed region. Correlation maps were extracted from each participant for each contrast of interest (e.g., correlations during high-risk decisions greater than correlations during low-risk decisions), and group analyses were conducted the same way as with standard fMRI group analyses: using one-sample *t* tests to test whether the parameter estimate at each voxel across participants was significantly different from zero. Regions exhibiting significant correlations were identified by thresholding the corresponding *t* maps at a two-tailed threshold of $P < .001$ with a cluster threshold of 6 contiguous voxels. In these analyses, a positive activation indicates that activity in that region correlates positively with activity in the seed region during the decision phase, and a negative activation indicates that activity in that region correlates negatively with activity in the seed region during the decision phase. We note that correlations between high-risk and low-risk averaged time courses within ACC and OFC were not significant (r values = −.20, .23; P values = .53, .46, respectively).

3. Results

3.1. Behavioral results

Participants took on average less time to indicate a high-risk relative to a low-risk decision (538 ms ± 83 and

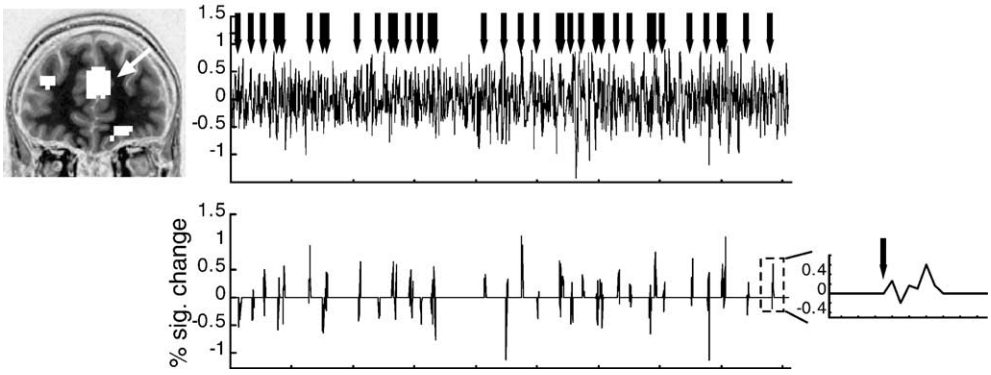

Fig. 1. Connectivity analysis regressors. Activity from a seed region (top left) is extracted for each subject (top middle), events of interest are identified (arrows indicate times when high-risk decisions were chosen), and activity during 6 TRs following each event is used as an independent variable in a GLM (lower middle). Lower right displays a close-up of the last event of interest.

594 ms ± 94, mean ± SEM, t_{15} = 5.18, P < .01). Although they were not more likely to choose the low-risk decision than the high-risk decision (48% ± 3.6 versus 52% ± 3.6, mean ± SEM, respectively, t_{15} = .53, ns), participants significantly avoided using a win–stay/lose–switch strategy (34% of trials [50% is no strategy use]; t_{15} = −9.47, P < .001).

3.2. fMRI results

In the present report, we focus our analyses on the decision phase of the task. Our first set of analyses concerned brain regions that exhibited a significant difference in activity when participants chose the high-risk decision versus when they chose the low-risk decision. As seen in Fig. 2, significantly greater activity was observed during high-risk vs. low-risk decisions in right OFC (BA 11), ACC (BA 24/32), and right PFC (BA 45). No areas of the brain exhibited greater activity during low-risk compared to high-risk trials. Also displayed in Fig. 2 are the averaged time courses and regression beta weights (relative to the ITI) in ACC and OFC during high- and low-risk decisions. MNI coordinates of these and all other activations reported in this paper are presented in Table 1.

Our next set of analyses concerned functional connectivity. We used the ACC and OFC regions identified above as seed regions to examine in which brain regions did activity significantly correlate with activity in ACC and OFC. For each region, we first examined connectivity during high-risk and low-risk trials separately and then tested whether there was a significant difference between connectivity during these two conditions.

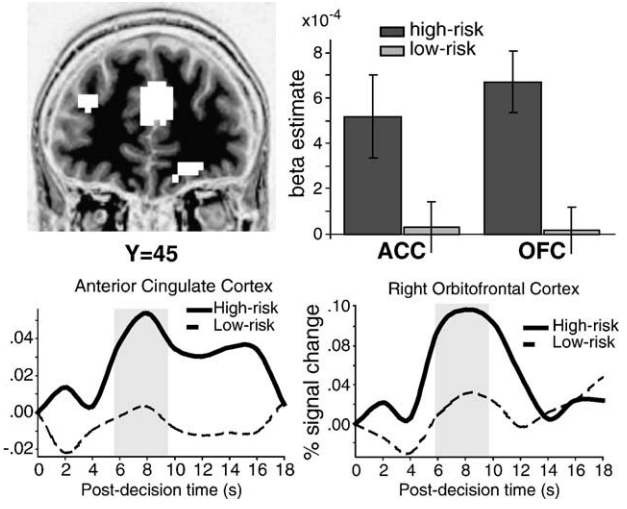

Fig. 2. Regions of the brain exhibiting significantly greater activity during high-risk compared to low-risk decisions. Top right shows a bar graph depicting the beta values (GLM parameter estimates) for high- and low-risk decisions in ACC and OFC, relative to the ITI. Error bars represent standard errors about the mean across subjects. Bottom left and right show time course plots of activity from ACC and OFC, respectively. *Y* axis represents percent signal change. Gray bars indicate expected time of HRF peak following the decision.

We first examined connectivity with the ACC (Fig. 3). Similar patterns of connectivity with the ACC emerged during both high- and low-risk decisions, including the extent of the cingulate gyrus (extending into medial PFC), bilateral striatum, parietal cortex (BA 39), and dorsolateral PFC (BA 45). We also observed significant negative correlations with the ACC in right amygdala, supplementary motor area (BA 6), parietal cortex (BA 7), and cerebellum. We next examined regions that showed a significant difference in correlation with ACC during high- vs. low-risk trials. Although no significant differences in connectivity were observed using a threshold of P < .001, at a two-tailed threshold of P < .005, several regions exhibited significantly greater connectivity during high- compared with low-risk decisions, including left nucleus accumbens, medial and lateral OFC, supplementary motor area (SMA; BA 6), anterior PFC, and cerebellum (see Fig. 3b).

We next tested for areas of the brain in which activity correlated significantly with activity in OFC (Fig. 4). During both high- and low-risk decisions, we observed significant correlations in PFC regions including bilateral OFC (BA 11), frontopolar PFC (BA 10/46), dorsolateral PFC (BA 46/9), dorsomedial PFC (extending into ACC; BA 24/32), parietal cortex (BA 40/7), and temporal cortex (BA 20/37). We additionally observed negative correlations with right superior and medial temporal gyri (BA 41s and 21). During high-risk but not low-risk decisions, we observed significant correlations in posterior cingulate (BA 23). However, when directly comparing connectivity during high- and low-risk decisions, no significant differences emerged.

Fig. 5 displays a double overlay map of regions in which significant correlations were observed with OFC (red), ACC (purple), and both (green) during high-risk decisions. As seen in the figure, largely non-overlapping regions were correlated with OFC and ACC. Whereas ACC activity was highly correlated with the striatum and medial PFC structures such as the cingulate and medial PFC, and with posterior parietal regions, OFC activity was more correlated with dorsolateral PFC and dorsal parietal regions. However, some overlaps were observed in superior medial PFC (BA 32) and posterior cingulate (BA 23).

4. Discussion

In the present study, we sought to investigate the roles of ACC and OFC during a decision-making task. Consistent with previous reports, we found that both ACC and OFC exhibited significantly greater activation when participants made high-risk relative to low-risk decisions [24,49]. Furthermore, networks of cortical and subcortical regions exhibited significant functional connectivity with these regions during these decisions.

Table 1
List of peak voxels for activation clusters

Region	BA	*t*	X	Y	Z
High > low risk					
R. orbital frontal	11	4.72	24	39	−12
R. cingulate	32	4.48	7	43	23
R. middle frontal	45	4.47	52	33	20
L. inferior parietal lobule	40	4.98	−63	−33	51
L. lateral temporal	37	5.23	−51	−54	−20
Connectivity with ACC: high-risk					
L. middle temporal	20	6.78	−56	−33	−14
R. middle temporal	21	8.82	53	−26	−6
Medial OFC	11	10.94	0	50	−9
L. inferior frontal	47	5.99	−46	36	−19
R. inferior frontal	47	5.45	52	29	−3
R. middle frontal	45	5.28	57	27	14
L. middle frontal	45	4.87	−54	22	9
L. striatum		9.19	−11	15	−4
R. striatum		10.40	7	15	3
Posterior cingulate	23	11.21	7	−54	29
L. inferior parietal	39	16.36	−49	−64	29
R. inferior parietal	39	12.61	57	−62	30
Anterior cingulate	24	44.15	3	46	25
L. precentral	43	5.10	−58	−9	33
L. middle frontal	44	3.91	−36	13	30
R. middle frontal	44	6.92	46	20	37
Dorsal cingulate	23	7.88	8	−18	47
R. amygdala		−4.67	18	1	−23
L. cerebellum		−6.17	−38	−47	−40
R. cerebellum		−5.53	46	−54	−31
R. fusiform	19	−5.21	20	−50	−15
L. middle occipital	19	−5.10	−43	−65	−5
L. temporal pole	48	−4.13	−61	6	2
L. posterior parietal	7	−4.56	−14	−72	51
R. posterior parietal	7	−7.35	18	−76	57
L. SMA	6	−4.99	−20	−3	59
R. SMA	6	−5.31	24	1	59
Connectivity with ACC: low-risk					
R. superior temporal	39	14.80	−52	−70	25
L. superior temporal	39	10.74	60	−70	32
R. orbitofrontal	11	7.13	−7	13	−17
R. inferior frontal	47	4.49	−52	18	−3
R. middle frontal	45	4.99	57	23	8
L. middle frontal	45	5.23	−52	19	18
L. caudate	25	6.87	−10	14	−3
R. caudate	25	7.93	4	11	−3
L. cingulate	32	40.43	0	42	21
L. frontal operculum	44	5.69	−52	19	14
R. inferior frontal	38	6.06	46	28	−17
R. middle frontal	44	4.58	46	18	39
L. superior frontal	32	28.40	−3	53	21
R. middle occipital	39	13.47	49	−66	28
L. inferior temporal	20	4.78	−63	−38	−17
R. inferior temporal	20	5.93	56	−28	−17
R. amygdala		−4.94	18	1	−23
R. parietal	7	−6.90	−14	−66	60
L. parietal	7	−6.82	18	−77	53
R. SMA	6	−6.73	32	−7	74
L. cerebellum		−8.55	−42	−48	−38
R. cerebellum		−9.29	42	−45	−42
R. postcentral	5	−6.32	11	−52	74
L. SMA	6	−5.76	−21	−2	60
L. precentral	6	−8.56	−22	−6	67
L. superior parietal	7	−6.45	−13	−66	56
R. superior parietal	7	−5.34	17	−55	70
R. precuneus	7	−4.54	14	−73	60

Table 1 (*continued*)

Region	BA	*t*	X	Y	Z
Connectivity with ACC: low-risk					
L. fusiform	36	−5.18	−42	67	−6
L. inferior temporal	37	−8.97	−45	−45	−24
Connectivity with ACC: high > low risk ($P < .005$)					
Medial orbital	11	4.40	0	53	−15
R. orbital frontal	11	3.99	25	43	−11
L. ventral striatum	−7	3.46	−7	10	−3
L. superior frontal	6	4.66	−18	0	52
R. superior frontal	9	3.87	3	60	43
L. inferior temporal	20	4.65	−48	−14	23
L. cerebellum		4.75	−38	−75	−27
R. fusiform	37	4.48	40	−42	−6
Connectivity with OFC: high-risk					
R. superior frontal	46	7.27	30	58	26
L. superior frontal	46	4.73	−26	62	20
R. middle frontal	9	4.36	39	33	36
L. middle frontal	46	4.36	−37	36	42
Middle frontal	32	6.54	5	25	44
L. inferior temporal	20	5.73	−66	−45	−24
L. superior parietal	7	5.23	−24	−80	49
Cingulate	23	5.22	3	−41	49
R. caudate		4.72	11	23	8
R. precuneus		5.61	11	−51	53
L. angular	7	6.09	−30	−66	49
L. orbitofrontal	11	9.54	−24	39	−21
R. orbitofrontal	11	5.72	21	37	−11
L. cerebellum	18	4.23	−5	−79	−21
R. inferior temporal	20	5.43	59	−24	−24
Posterior cingulate	23	4.93	0	−35	34
R. cingulate	24	7.30	4	21	49
SMA	32	4.49	−3	27	46
R. inferior temporal	37	4.87	56	−66	−21
L. inferior parietal	40	5.39	−45	−49	42
R. angular	40	7.70	39	−56	42
R. middle frontal	46	9.74	32	53	28
L. superior temporal	41	−5.98	49	−38	17
L. middle temporal	21	−4.90	−50	−2	−17
R. middle temporal	20	−4.97	40	4	−24
Connectivity with OFC: low-risk					
R. superior frontal	46	6.53	27	60	27
L. superior frontal	46	5.13	−25	62	24
R. middle frontal	9	4.05	37	33	35
L. middle frontal	46	5.06	−34	31	45
Middle frontal	32	5.43	3	24	44
L. cerebellum		5.17	−4	−79	−25
L. superior parietal		7.46	−28	−72	49
R. precuneus		4.60	0	−56	74
R. superior frontal	6	5.91	21	11	60
L. precentral	6	4.69	−52	9	42
L. SMA	6	4.68	−26	7	65
R. SMA	6	7.17	9	24	53
L. middle occipital	7	6.20	−24	−60	42
R. superior parietal	7	7.21	25	−73	49
L. middle frontal	8	8.60	−26	7	60
Superior frontal	8	6.34	0	28	46
R. middle frontal	9	7.10	43	28	46
L. middle frontal	10	5.99	−35	60	11
L. orbitofrontal	11	10.45	−21	39	−21
R. orbitofrontal	11	50.80	18	42	−21
L. inferior temporal	20	5.45	−59	−35	−24
R. inferior temporal	20	6.09	56	−38	−21
R. angular	39	6.95	39	−59	42

(continued on next page)

Table 1 (*continued*)

Region	BA	*t*	X	Y	Z
Connectivity with OFC: low-risk					
R. inferior parietal	40	6.29	46	−49	49
L. middle frontal	44	6.20	−49	28	35
R. inferior frontal	45	5.10	49	42	2
R. inferior frontal	45	7.96	49	35	28
R. middle frontal	45	7.11	42	52	21
L. middle frontal	46	9.15	−45	49	14
L. superior temporal	48	−5.19	−41	−23	16
R. superior temporal	48	−5.50	42	−16	19

L. = left hemisphere; R. = right hemisphere. BA = Brodmann's areas.

4.1. Anterior cingulate cortex

Our finding that ACC was more active during high- compared to low-risk decisions is consistent with other reports of the ACC and decision-making [9,24,49]. It is noteworthy that ACC activity was not observed during low-risk decisions, either in the time courses or when comparing activity to that during the ITI. This suggests that, in our task, ACC activity did not reflect processes related to a motor response or to general task-related attentional processing, but rather a representation of a relatively high-risk potential reward. The ACC has been previously described as having two main functionally divisible sections, ventral and dorsal, which process emotional and cognitive information, respectively [10]. In our study, as in those of Ernst et al. and Rogers et al. [24,49], high-risk decision-related ACC activity was observed in the more ventral aspect, whereas more dorsal regions of ACC tend to be activated during error monitoring or when processing conflicting information [7,9]. Thus, it appears that the emotional/cognitive distinction between subregions of the ACC may extend into decision-making that does or does not involve emotional considerations. Due to our experimental design, we were not able to distinguish whether the ACC activation was driven by a relatively small chance of a large reward, or a relatively large chance of a failure to receive a reward, or the combination of both.

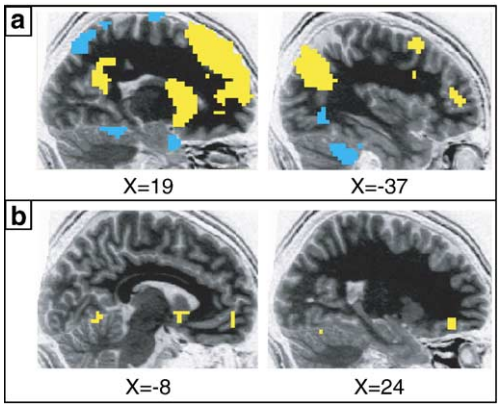

Fig. 3. Connectivity with the ACC. (a) Connectivity with the ACC is shown during high-risk decisions, although during low-risk decisions, the topographical distribution of connectivity was very similar (see Results and Table 1). Yellow voxels indicate that activity correlated positively with ACC during high-risk decisions, blue voxels indicate that activity correlated negatively. (b) Areas that showed significantly greater connectivity with ACC during high-risk compared with low-risk trials ($P < .005$).

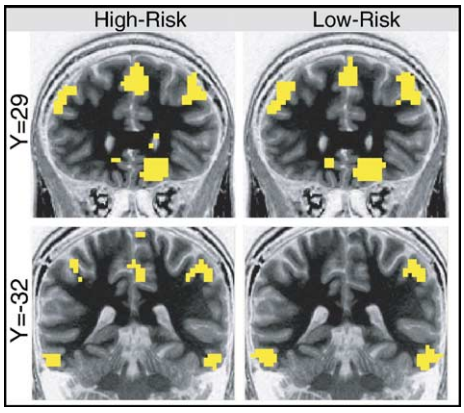

Fig. 4. Areas that exhibited significant connectivity with OFC during high-risk (left) and low-risk (right) decisions. Conventions are as in Fig. 3.

Many investigations into the functions of the ACC concern cognitive control and monitoring behavior for response conflicts [7,59]. Findings from these studies might lead one to conclude that our participants simply felt more conflict when they chose high-risk decisions over low-risk decisions. Although we did not collect online or post-experimental measures of whether participants experienced any differential levels of conflict during the experiment, several considerations suggest that increased response conflict cannot completely account for the ACC activation observed here. First, the locus of our activation is relatively ventral compared with the more dorsal (i.e., closer to SMA) ACC activations typically reported in studies of conflict monitoring [30,59]. Second, response times for high-risk decisions were shorter than those for low-risk decisions—opposite of what would be expected if high-risk decisions were associated with increased conflict. Third, it is likely that low-risk decisions were also associated with some amount of conflict because participants still had to make a decision under uncertain conditions. The conflict monitoring theory would therefore predict some amount of ACC activation even during low-risk decisions. However, the ACC cluster identified in the high- vs. low-risk contrast was not significantly active during low-risk trials (see time

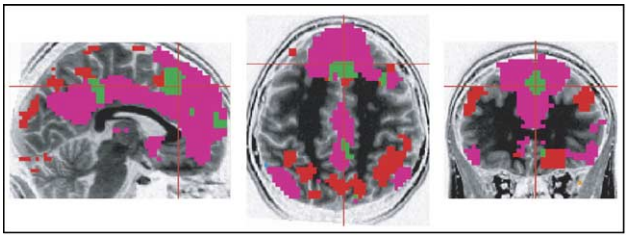

Fig. 5. Double overlay depicting regions exhibiting significant connectivity with ACC (purple), OFC (red), and both ACC and OFC (green). Slices correspond to MNI coordinates [5,9,15] (*XYZ*).

course and bar graph plots in Fig. 2). This pattern of ACC activation also is not consistent with a role for this region in considering or debating between decision options, because these processes would have occurred during low-risk trials as well. Thus, the ACC activation was likely driven largely by representations of risky potential rewards associated with increased potential failure to obtain a reward [24]. We note that, in our study, as well as that of Rogers et al. [49], significant activation was not observed in the nucleus accumbens when comparing high- vs. low-risk decisions, in contrast to findings reported by Ernst et al. [24]. This difference might be due to the higher reward levels presented to subjects in the Ernst et al. study ($7 compared to $2.50 in our study and $0.80 in Rogers et al.). Indeed, other studies have demonstrated a link between activity in the nucleus accumbens and magnitude of monetary rewards [32].

Connectivity analyses using ACC activation as a seed region revealed that, consistent with known neuroanatomical connections of ACC, an extensive network of regions including the striatum, amygdala, cingulate gyrus, medial and lateral PFC, and parietal cortex exhibited activity that correlated significantly with that in ACC [37,60]. The correlations in the striatum highlight the emotional aspect of this task and the representation of high-risk reward in the ACC, and the correlations in more dorsal regions of PFC and parietal cortex likely reflect cognitive task-related functions that ACC may influence, such as error monitoring and response preparation [59]. We found a negative correlation between activity in ACC and right amygdala, supporting the idea that these two regions work in conjunction during conditioning and reward learning tasks [46,56]. Consistent with our findings, Ochsner et al. have reported an inverse relationship between activation of the amygdala and regions in PFC [38,39]. Specifically, they found that activity in medial PFC regions correlated negatively with activity in the amygdala during self-focused emotional regulation [39]. Given both ACC and amygdala's role in regulating emotional and physiological states [16,46] seems likely that, during risky decision-making, these two regions work in conjunction to regulate emotional states related to high-risk decision-making [3]. Ochsner et al. have suggested that activation of the right amygdala reflects regulation of emotional and arousing stimuli, such as might have been elicited in our study when participants choose high-risk decisions [17,16].

At a slightly lower statistical threshold ($P < .005$, two-tailed), several regions of the brain exhibited significantly increased connectivity with ACC during high-risk compared to low-risk decisions, including the left nucleus accumbens, OFC, and dorsal PFC regions. Processing in all of these regions is related to rewards and reward-seeking behavior, as well as in using reward information to guide future decisions [13]. Available evidence strongly implicates the ACC in behavioral inhibition and cognitive control [7,10,30], and it is possible that one mechanism for this control is through modulating the activity of neural populations in other regions of the brain. Increased functional coupling of ACC with these regions may thus reflect a control mechanism by which ACC regulates emotional, attentional, and physiological processes during reward-based decision-making [17]. Further studies will need to be conducted to more closely examine the relationship between connectivity among these regions, levels of uncertainty, and attentional and physiological arousal.

4.2. Orbitofrontal cortex

Our finding that OFC was significantly more active during high- vs. low-risk decisions is consistent with a growing literature on the link between OFC functioning and reward-related decision-making [6,41,52]. For example, patients with lesions to OFC tend to prefer risky decision strategies, even when those strategies are associated with long-term losses [6,4]. This finding is sometimes interpreted to mean that OFC is critical for relearning reward-based associations when reward contingencies change [15,52] or that OFC is involved in dynamically updating behavior according to ongoing reinforcements [14]. As with the ACC, no activity was observed in OFC during low-risk decisions, as seen in the time course of activity in Fig. 2, suggesting that OFC is preferentially involved in risky decision-making, and not simply situations in which a decision must be made. This activation may thus reflect processes related to forming or considering associations between relatively risky decisions made and the possible rewards or failures that can be received. The right-lateralized OFC activation is consistent both with other neuroimaging studies of decision-making [17,22,49] and with observations that patients with right OFC damage have greater decision-making impairments than those with left OFC damage [57]. OFC activity can be observed during both choice selection, as we and others have observed [49], as well as during outcome evaluation [21,40], suggesting functional subdivisions within the OFC [41]. Its role during choice selection may be related to forming or considering associations between stimuli or behavior and rewards, whereas its role during outcome evaluation may be more related to confirming or updating those associations.

Connectivity analyses using OFC as the seed region revealed that, consistent with known anatomical pathways, OFC activity during decision-making was significantly correlated with activity in dorsal and medial PFC (extending into ACC), parietal and temporal cortices, as well as the striatum [11,36]. Consistent with this, other groups have noted large networks of brain regions engaged during decision-making tasks that incorporate regions in PFC, parietal, and temporal cortices [23,24,42]. Although patients with damage to OFC are often observed to perservate in risk-taking behavior despite

ongoing losses, few reports have noted that patients with more extensive damage to dorsal PFC regions (sparing OFC) show similar impairments in risk-taking tasks [26,35,55]. Given the tight anatomical and functional connections between OFC and dorsal PFC, it is possible that damage to dorsal PFC regions additionally disrupts processes in OFC, thus causing the observed impairments. These couplings of activity with OFC may reflect both cognitive aspects of decision-making, such as planning and working memory in PFC and parietal cortex, and more emotional aspects of decision-making, such as reward calculation and prediction in the striatum. For example, parietal cortex has been identified as being critical for computations related to choosing one among several decision options, especially when those decisions can lead to rewards [19,50].

We additionally observed that the posterior cingulate exhibited significant connectivity during high-risk but not low-risk trials. Several experiments have shown that the posterior cingulate is involved in making semantic or categorical decisions about emotionally-laden words and images [34,61]. Our finding suggests that this region may participate in other kinds of decisions as well, and increased correlations in posterior cingulate with OFC may reflect addition emotion processing related to high-risk decisions. However, we note that this effect was not significant in a direct comparison between connectivity during high- and low-risk decisions. Indeed, no areas of the brain exhibited significantly different correlations with OFC between high- and low-risk decisions, in contrast to the corresponding analysis using ACC as the seed region. Although this seems to suggest that activity in OFC distinguishes high- from low-risk decisions yet its connectivity with other regions is relatively constant across these two types of decisions, one should be cautious when interpreting null findings because it is possible that changes in connectivity with OFC during different decisions are more subtle than those associated with ACC, and therefore more difficult to detect.

4.3. Relationship between OFC and ACC

As seen in both the time courses and the comparison of the beta values compared to the ITI in Fig. 2, activity in OFC and ACC appeared very similar: Both regions were preferentially activated during the selection of a high-risk, but not low-risk, decisions. Thus, based on these findings alone, one is not able to distinguish between possible differences in functions between these two regions. However, inspection of connectivity analyses using these two areas as seed regions revealed large differences in regions of the brain that exhibited significant functional connectivity, with little overlap between them. Based on these results, it seems that, whereas ACC engages a neural network involved in behavioral control, error monitoring, and reward calculations, OFC engages a neural network involved in planning, working memory, and decision calculations. There was some overlap in connectivity results, however, particularly in dorsal ACC/medial PFC (BA 32) and posterior ACC (BA 23), suggesting some overlap of function, possibly related to planning and controlling motor responses [54] or emotional aspects of making decisions [34].

4.4. Caveats and conclusions

We acknowledge a few caveats and limitations of the present study. First, as with many types of fMRI analyses, our connectivity data are inherently correlational, and therefore no strong claims can be made about the directions of influence of one brain region on another. Furthermore, although correlations between activities in different brain regions suggest functional connectivity, it is possible that distinct brain regions could exhibit correlated time courses without being functionally connected. However, we note that, at our threshold, activity in primary visual or motor cortices was not significantly correlated with activity in OFC and ACC, demonstrating that this analysis procedure is not modeling general task-related activity changes, and is therefore not redundant with the standard GLM approach to modeling increased activity in one condition over another. Second, although we and others [17,24,48] have used similar paradigms to distinguish between activity to different closely spaced events, it is possible that some activities related to processes occurring during outcome anticipation were modeled into the decision covariates. However, we note that distinct networks of brain regions can be observed when comparing activity during the decision and anticipation phases (Cohen and Ranganath, unpublished observations; [25]). Third, our experiment focused on a decision between economically equivalent choices to obtain rewards. Further research will be required before generalizing our findings to other decision-making situations, such as those that involve losses or reward-based learning [6]. Finally, there are several ways of assessing functional connectivity using fMRI data [8], and it is not known whether other methods would reveal similar results. However, our methodology has been used previously [45], is similar to other methods of functional connectivity [27], and our findings are consistent with known anatomical connections of OFC and ACC [11,36,60].

In conclusion, we have demonstrated that ACC and OFC are significantly engaged when choosing high-risk over low-risk decisions. Using additional techniques to examine functional connectivity, we found that, although ACC and OFC exhibited similar patterns of activation and time courses, these regions exhibited distinct patterns of functional connectivity, suggesting that they play different, and perhaps complementary, roles in decision-making. Future studies might benefit from using connectivity analyses to distinguish between functions of different brain regions that otherwise exhibit similar patterns of task-related activity.

References

[1] G.K. Aguirre, E. Zarahn, M. D'Esposito, Empirical analyses of BOLD fMRI statistics. II. Spatially smoothed data collected under null-hypothesis and experimental conditions, NeuroImage 5 (3) (1997) 199–212.

[2] G.K. Aguirre, E. Zarahn, M. D'Esposito, The variability of human. BOLD hemodynamic responses, NeuroImage 8 (4) (1998) 360–369.

[3] A. Bechara, et al., Deciding advantageously before knowing the advantageous strategy, Science 275 (5304) (1997) 1293–1295.

[4] A. Bechara, et al., Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making, J. Neurosci. 19 (13) (1999) 5473–5481.

[5] A. Bechara, H. Damasio, A.R. Damasio, Emotion, decision making and the orbitofrontal cortex, Cereb. Cortex 10 (3) (2000) 295–307.

[6] A. Bechara, H. Damasio, A.R. Damasio, Risky business: emotion, decision-making, and addiction, J. Gambl. Stud. 19 (1) (2003) 23–51.

[7] M.M. Botvinick, et al., Conflict monitoring and cognitive control, Psychol. Rev. 108 (3) (2001) 624–652.

[8] C. Buchel, Perspectives on the estimation of effective connectivity from neuroimaging data, Neuroinformatics 2 (2) (2004) 169–174.

[9] G. Bush, et al., Dorsal anterior cingulate cortex: a role in reward-based decision making, Proc. Natl. Acad. Sci. U. S. A. 99 (1) (2002) 523–528.

[10] G. Bush, P. Luu, M.I. Posner, Cognitive and emotional influences in anterior cingulate cortex, Trends Cogn. Sci. 4 (6) (2000) 215–222.

[11] C. Cavada, et al., The anatomical connections of the macaque monkey orbitofrontal cortex. A review, Cereb. Cortex 10 (3) (2000) 220–242.

[12] Y. Chudasama, et al., Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity, Behav. Brain Res. 146 (1–2) (2003) 105–119.

[13] M.X Cohen, C. Ranganath, Behavioral and neural predictors of upcoming decisions. Cognitive, Behavioral, and Affective Neuroscience, in press.

[14] M.X Cohen, R. Ranganath, Behavioral and neural predictors of upcoming decisions. Cognitive, Behavioral, and Affective Neuroscience, under review.

[15] R. Cools, et al., Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging, J. Neurosci. 22 (11) (2002) 4563–4567.

[16] H.D. Critchley, et al., Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans, J. Physiol. 523 (Pt. 1) (2000) 259–270.

[17] H.D. Critchley, C.J. Mathias, R.J. Dolan, Neural activity in the human brain relating to uncertainty and arousal during anticipation, Neuron 29 (2) (2001) 537–545.

[18] A.E. Desjardins, K.A. Kiehl, P.F. Liddle, Removal of confounding effects of global signal in functional MRI analyses, NeuroImage 13 (4) (2001) 751–758.

[19] M.C. Dorris, P.W. Glimcher, Activity in posterior parietal cortex is correlated with the relative subjective desirability of action, Neuron 44 (2) (2004) 365–378.

[20] T.J. Druzgal, M. D'Esposito, Dissecting contributions of prefrontal cortex and fusiform face area to face working memory, J. Cogn. Neurosci. 15 (6) (2003) 771–784.

[21] R. Elliott, K.J. Friston, R.J. Dolan, Dissociable neural responses in human reward systems, J. Neurosci. 20 (16) (2000) 6159–6165.

[22] R. Elliot, et al., Differential response patterns in the human striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study, J. Neurosci. 2003 (23) (2003) 303–307.

[23] M. Ernst, et al., Decision-making in a risk-taking task: a PET study, Neuropsychopharmacology 26 (5) (2002) 682–691.

[24] M. Ernst, et al., Choice selection and reward anticipation: an fMRI study, Neuropsychologia 42 (12) (2004) 1585–1597.

[25] J.S. Feinstein, et al., Dissecting decision-making: differential involvement of the prefrontal cortex and anterior insula in action selection, anticipation, and outcome evaluation, Program No. 372.3.2004 Abstract Viewer and Itinerary Planner, Society for Neuroscience, Washington, DC, 2004.

[26] L.K. Fellows, M.J. Farah, Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans, Cereb. Cortex 24 (2004) 24.

[27] K.J. Friston, et al., Psychophysiological and modulatory interactions in neuroimaging, NeuroImage 6 (3) (1997) 218–229.

[28] D.A. Handwerker, J.M. Ollinger, M. D'Esposito, Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses, NeuroImage 21 (4) (2004) 1639–1651.

[29] A. Izquierdo, E.A. Murray, Combined unilateral lesions of the amygdala and orbital prefrontal cortex impair affective processing in rhesus monkeys, J. Neurophysiol. 91 (5) (2004) 2023–2039 (Electronic publication, 2004 Jan 7).

[30] J.G. Kerns, et al., Anterior cingulate conflict monitoring and adjustments in control, Science 303 (2004) 1023–1026.

[31] P. Kirsch, et al., Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study, NeuroImage 20 (2) (2003) 1086–1095.

[32] B. Knutson, et al., Anticipation of increasing monetary reward selectively recruits nucleus accumbens, J. Neurosci. 21 (16) (2001) RC159.

[33] D.C. Krawczyk, Contributions of the prefrontal cortex to the neural basis of human decision making, Neurosci. Biobehav. Rev. 26 (6) (2002) 631–664.

[34] R.J. Maddock, The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain, Trends Neurosci. 22 (7) (1999) 310–316.

[35] F. Manes, et al., Decision-making processes following damage to the prefrontal cortex, Brain 125 (Pt. 3) (2002) 624–639.

[36] R.J. Morecraft, C. Geula, M.M. Mesulam, Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey, J. Comp. Neurol. 323 (3) (1992) 341–358.

[37] S.Y. Musil, C.R. Olson, Organization of cortical and subcortical projections to anterior cingulate cortex in the cat, J. Comp. Neurol. 272 (2) (1988) 203–218.

[38] K.N. Ochsner, et al., Rethinking feelings: an FMRI study of the cognitive regulation of emotion, J. Cogn. Neurosci. 14 (8) (2002) 1215–1229.

[39] K.N. Ochsner, et al., For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion, NeuroImage 23 (2) (2004) 483–499.

[40] J. O'Doherty, et al., Abstract reward and punishment representations in the human orbitofrontal cortex, Nat. Neurosci. 4 (1) (2001) 95–102.

[41] J. O'Doherty, et al., Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices, J. Neurosci. 23 (21) (2003) 7931–7939.

[42] M.P. Paulus, et al., Prefrontal, parietal, and temporal cortex networks underlie decision-making in the presence of uncertainty, NeuroImage 13 (1) (2001) 91–100.

[43] M.P. Paulus, et al., Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism, NeuroImage 19 (4) (2003) 1439–1448.

[44] A. Peru, G. Pavesi, M. Campello, Impairment of executive functions in a patient with a focal lesion in the anterior cingulate cortex. Evidence from neuropsychological assessment, Funct. Neurology 19 (2) (2004) 107–111.

[45] L. Pessoa, et al., Neural correlates of visual working memory: fMRI amplitude predicts task performance, Neuron 35 (5) (2002) 975–987.

[46] E.A. Phelps, et al., Extinction learning in humans: role of the amygdala and vmPFC, Neuron 43 (6) (2004) 897–905.

[47] C. Ranganath, M. D'Esposito, Medial temporal lobe activity associated with active maintenance of novel information, Neuron 31 (5) (2001) 865–873.

[48] C. Ranganath, et al., Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval, J. Neurosci. 24 (16) (2004) 3917–3925.
[49] R. Rogers, et al., Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition, Biol. Psychiatry 55 (2004) 594–602.
[50] J.D. Roitman, M.N. Shadlen, Response of neurons in the lateral intraparietal area during a combined visual discrimination reaction time task, J. Neurosci. 22 (21) (2002) 9475–9489.
[51] E.T. Rolls, The orbitofrontal cortex and reward, Cereb. Cortex 10 (3) (2000) 284–294.
[52] E.T. Rolls, The functions of the orbitofrontal cortex, Brain Cogn. 55 (1) (2004) 11–29.
[53] C. Rorden, M. Brett, Stereotaxic display of brain lesions, Behav. Neurol. 12 (4) (2000) 191–200.
[54] M.F. Rushworth, et al., Action sets and decisions in the medial frontal cortex, Trends Cogn. Sci. 8 (9) (2004) 410–417.
[55] A.G. Sanfey, et al., Phineas gauged: decision-making and the human prefrontal cortex, Neuropsychologia 41 (9) (2003) 1218–1229.
[56] G. Schoenbaum, A.A. Chiba, M. Gallagher, Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training, J. Neurosci. 20 (13) (2000) 5179–5189.
[57] D. Tranel, A. Bechara, N.L. Denburg, Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing, Cortex 38 (4) (2002) 589–612.
[58] V. van Veen, et al., Anterior cingulate cortex, conflict monitoring, and levels of processing, NeuroImage 14 (6) (2001) 1302–1308.
[59] V. van Veen, C.S. Carter, The anterior cingulate as a conflict monitor: fMRI and ERP studies, Physiol. Behav. 77 (4–5) (2002) 477–482.
[60] B.A. Vogt, D.N. Pandya, Cingulate cortex of the rhesus monkey: II. Cortical afferents, J. Comp. Neurol. 262 (2) (1987) 271–289.
[61] B.A. Vogt, J.R. Absher, G. Bush, Human retrosplenial cortex: where is it and is it involved in emotion? Trends Neurosci. 23 (5) (2000) 195–197.
[62] M.E. Walton, et al., Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions, J. Neurosci. 23 (16) (2003) 6475–6479.