

## Distinct Roles of Prefrontal Cortical Subregions in the Iowa Gambling Task

Natalia S. Lawrence<sup>1,2,3</sup>, Fabrice Jollant<sup>1,4</sup>, Owen O'Daly<sup>2</sup>,  
Fernando Zelaya<sup>2</sup> and Mary L. Phillips<sup>1,5</sup>

<sup>1</sup>King's College London, Section of Neuroscience and Emotion, Division of Psychological Medicine and Psychiatry,

<sup>2</sup>Department of Clinical Neuroscience, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK, <sup>3</sup>Wales Institute of Cognitive Neuroscience, School of Psychology, Cardiff

University, Cardiff, UK, <sup>4</sup>Université Montpellier 1, Inserm U888, Montpellier, CHU Montpellier, Montpellier France and

<sup>5</sup>Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Natalia S. Lawrence and Fabrice Jollant contributed equally to this article.

**The Iowa Gambling Task (IGT)** assesses decision-making under initially ambiguous conditions. Neuropsychological and neuroimaging data suggest, albeit inconsistently, the involvement of numerous prefrontal cortical regions in task performance. To clarify the contributions of different prefrontal regions, we developed and validated a version of the IGT specifically modified for event-related functional magnetic resonance imaging. General decision-making in healthy males elicited activation in the ventromedial prefrontal cortex. Choices from disadvantageous versus advantageous card decks produced activation in the medial frontal gyrus, lateral orbitofrontal cortex (OFC), and insula. Moreover, activation in these regions, along with the pre-supplementary motor area (pre-SMA) and secondary somatosensory cortex, was positively associated with task performance. Lateral OFC and pre-SMA activation also showed a significant modulation over time, suggesting a role in learning. Striato-thalamic regions responded to wins more than losses. These results both replicate and add to previous findings and help to reconcile inconsistencies in neuropsychological data. They reveal that deciding advantageously under initially ambiguous conditions may require both continuous and dynamic processes involving both the ventral and dorsal prefrontal cortex.

**Keywords:** ambiguity, decision-making, medial frontal gyrus, orbitofrontal cortex, pre-supplementary motor area, wins

### Introduction

The Iowa Gambling Task (IGT; Bechara et al. 1994) is an extremely widely and frequently used neuropsychological test of decision-making ability under initially ambiguous conditions (Brand et al. 2007). The test simulates real-life decision making by testing the ability of participants to learn to sacrifice immediate rewards in favor of long-term gain. Deficits in task performance have been demonstrated in diverse psychiatric groups, including pathological gamblers (Cavedini et al. 2002a), patients with Obsessive-Compulsive Disorder (Cavedini et al. 2002b, Cavallaro et al. 2003, Lawrence et al. 2006), patients with eating disorders (Cavedini et al. 2004), psychopathic (Mitchell et al. 2002), and substance-dependent individuals (Grant et al. 2000; Bechara and Damasio 2002) and suicide attempters (Jollant et al. 2005).

Evidence for the neurobiological basis of the IGT originates in the pioneering studies of Bechara et al. (Bechara et al. 1994, 1999), which demonstrated task deficits in patients with ventromedial prefrontal cortex (VM PFC) and amygdala lesions. Subsequent studies revealed a more specific role for the right

lateral orbitofrontal cortex (OFC) in IGT performance (Tranel et al. 2002) although some contest this functional specificity and suggest that more widespread prefrontal lesions in dorsolateral (Manes et al. 2002; Clark et al. 2003; Fellows and Farah 2005) and dorsomedial (Manes et al. 2002) regions also impair performance, albeit via different underlying mechanisms (Manes et al. 2002; Bechara 2004; Fellows and Farah 2005). Neuroimaging studies, primarily using positron emission tomography (PET), have confirmed activation of the VM PFC (Brodmann area [BA] 11, 47) during IGT performance and have additionally implicated a wider network of brain areas typically associated with working memory and visual attention, including the dorsolateral PFC, right anterior cingulate gyrus, right parietal cortex, thalamus, anterior insula, and cerebellum (Ernst et al. 2002). PET data further revealed that men and women show differences in regional activation during IGT performance (Bolla et al. 2004), with men activating the right lateral OFC (BA 10, 47) more than women, and women showing greater recruitment of left dorsolateral PFC, left medial frontal gyrus and temporal lobe than men. These sex differences in task-related activation could help to explain the sometimes reported male advantage on the IGT (Reavis and Overman 2001; Bolla et al. 2004; Overman et al. 2004; Lawrence et al. 2006). A key role for the right OFC in mediating successful IGT performance was also suggested by a positive correlation between activation in this region and performance, in a PET study in healthy controls and abstinent cocaine users (Bolla et al. 2003).

Whilst PET studies have been crucial in supporting the results of lesion studies regarding the neurobiological basis of the IGT, they have been constrained by the limited temporal resolution of PET, preventing clarification of regional activation associated with temporally distinct elements of IGT performance, such as responses during disadvantageous (or “risky”) versus advantageous (or “safe”) decisions, early versus late trials and the processing of wins versus losses. These elements of the IGT are associated with different skin conductance responses (Bechara et al. 1997, 1999; Lawrence et al. 2006), indicating that they are separable and may be related to distinct underlying neural mechanisms. In addition, PET studies have provided evidence that different brain regions are associated with improved performance and learning on the IGT, compared with task performance per se (Ernst et al. 2002), further suggesting that it is important to distinguish between the different task components. Functional magnetic resonance imaging (fMRI), with its superior

temporal and spatial resolution is ideally placed to overcome the limitations of PET and permit a more detailed examination of task-related functional neuroanatomy. To date, however, only 2 fMRI studies have examined blood oxygenation level-dependent (BOLD) activity during the original IGT, with one focusing on the decision-making phase (Fukui et al. 2005) and the other on the outcome phase (Windmann et al. 2006). Neither of these studies separated out all the task components described above, limiting their contrasts to comparing choices from risky versus safe decks (Fukui et al. 2005) and rewarding versus punishing outcomes (Windmann et al. 2006). Both studies confirmed a role for the medial frontal gyrus (BA 10) in the IGT and Fukui et al. (2005) revealed that this activation was positively related to task performance. Fukui et al. (2005) also suggested that poor signal recovery due to susceptibility artifacts in the OFC may have prevented a role for this more ventral PFC brain region from being observed in their study. A third fMRI study (Tanabe et al. 2007) used a heavily modified version of the IGT, in which a computer rather than the participant selected the cards, and revealed greater activation in healthy controls than in substance-dependent individuals in ventral medial frontal (BA 25/11) and right anterior prefrontal (BA 10) regions during active versus passive decision-making.

A large number of fMRI studies have used a range of gambling tasks similar to, but simpler than, the IGT to dissect the neural mechanisms of decision-making under conditions of risk or ambiguity, and during the processing of positive and negative reinforcement (see Ernst and Paulus 2005; Krain et al. 2006 for reviews). These studies have also suggested a key role for brain areas such as the OFC and medial frontal gyrus in making choices under risky conditions. However, whilst these simpler gambling tasks offer greater functional specificity for fMRI, many of them (often deliberately) fail to model the strategic learning dimension involved in the IGT, and this may be a key factor explaining poor task performance in groups with psycho- or neuropathology. For example, patients with focal dorsolateral and dorsomedial PFC lesions show a deficit on the IGT but not on the Cambridge Gamble and Risk tasks (which do not involve learning over trials) (Manes et al. 2002). Furthermore, these simpler gambling tasks may not model real-life decision-making as well as the IGT.

In the present study, we report an fMRI study of a novel version of the IGT, specifically adapted for use with event-related fMRI, which enables examination of the neural correlates associated with different task components, including decision making per se, choices from risky versus safe decks, successful task performance, learning over time, and receipt of wins versus losses. This study therefore builds upon previous fMRI studies of the IGT, which were limited to examining one aspect of the task. The current task promises to be a useful tool for exploring the specific neuroanatomical basis for decision-making problems in clinical populations. Current data are somewhat inconsistent but allow us to predict that:

- 1) Decision-making, that is, task performance per se, may be associated with VM PFC (and ventrolateral PFC) activity, in addition to other regions including dorsal PFC, right anterior cingulate gyrus, right parietal cortex, thalamus, anterior insula and cerebellum (confirming PET studies).

- 2) Choices from risky versus safe decks may be associated with VM PFC and, in particular, BA 10 activity (confirming Fukui et al. 2005).
- 3) Existing fMRI and PET data associating BA 10 and right OFC activation with successful task performance allow us to hypothesize that activation in both regions may be correlated with performance and additionally involved in task learning, in addition to being associated with risky decision-making trials.
- 4) In additional analyses, we also wished to examine brain activity related to wins versus losses in the IGT. We predict that wins will be associated with greater activation in ventral and dorsal striatum, and VM PFC (Delgado et al. 2000; Breiter et al. 2001; Rogers et al. 2004).

In view of the reported sex differences in IGT performance, we included only men in the current study.

## Materials and Methods

### Subjects

**Seventeen**, right-handed (Oldfield 1971) male volunteers participated in this study. Data from 2 subjects were excluded from analysis; 1 due to technical problems and 1 because of insufficient cards chosen (3) from the high-risk decks (A and B). The remaining 15 subjects were aged between 22 and 57 years (mean age = 32.7 years, SD = 10.1), with a mean education of 17.1 years (SD = 1.8) and a mean estimated verbal IQ (estimated using the National Adult Reading Test, Nelson 1982) of 118.76 (SD = 5.33). Subjects were all task-naïve, reported no history of any neurological or psychiatric disorder and no drug dependence by clinical screen (MINI 5.0.0; Sheehan et al. 1998) and were unmedicated at the time of the study. The Ethical Committee (Research) of the Maudsley Hospital and Institute of Psychiatry approved the study protocol and all subjects signed an informed consent form prior to their participation. Participants were paid £30 for their participation.

### Task

Subjects performed the computerized version of the IGT (Bechara et al. 2000) that was modified for rapid event-related fMRI (see below). The IGT (Bechara et al. 1994) simulates real-life decision making by testing the ability of participants to sacrifice immediate rewards in favor of long-term gain. Briefly, participants must select 100 cards, one at a time, from 4 identical-looking decks of cards, labeled A, B, C, and D. Participants are told that when they pick a card they will win some money but occasionally they will lose some money. They can select cards from any deck and the goal of the game is to win as much money as possible. Participants in our study (as in Bechara et al. 2000) were also told that "It is important to know that the computer does not make you lose money at random. However, there is no way for you to figure out when or why you lose money. You may find yourself losing money on all of the decks, but some decks will make you lose more than others. Even if you lost a lot of money, you can still win if you stay away from the worst decks." All participants began with a £2000 loan to play the game and wins and losses (in pounds Sterling) were tracked on screen using a green bar at the bottom of the screen. A red bar under the green bar reminded participants of how much money they had borrowed to play the game. Decks A and B were associated with large gains (£190, £200, and £210) and large losses (£240, £250, £260), whereas decks C and D provided smaller gains (£90, £100, and £110) and small losses (£40, £50, and £60). Decks A and B are "disadvantageous" (also referred to here as "risky") as they lead to a net loss over time, whereas decks C and D are "advantageous" (also referred to here as "safe") because they lead to a net gain. Task performance is measured by calculating the number of cards picked from advantageous decks (C + D) minus the number of cards picked from disadvantageous decks (A + B) in each block of 20 card selections. Healthy controls usually show an improvement in performance over the 5 blocks of 20 card selections, indicating that over time they are learning to avoid the

disadvantageous decks associated with larger losses. Participants were not paid any extra real money depending on their performance in this task.

The task was modified from the original computerized version to increase the number of similar trials in each condition (e.g., choices from risky and safe decks, trials resulting in wins and losses) in order to optimize statistical power for fMRI analysis. The modifications made were:

- 1) Reinforcement contingencies for decks A and B were similar to the original deck A (including a net loss of £250 over 10 cards), and those for decks C and D similar to the original deck C (a net gain of £250 over 10 cards). This change resulted in all 4 decks having the same mean frequency of wins to losses (50:50), which is equivalent to the frequency of punishment in the original IGT decks A and C. Decks B and D from the original task, which have infrequent very large losses, were therefore not represented in this version of the task. This modification resulted in roughly equal numbers of win and loss trials, optimizing the statistical comparison between these 2 conditions. The schedules of reinforcement for decks A and B, and C and D were equivalent but trials were presented in a different order. As choices from risky decks A and B (and safe decks C and D) were equivalent, this enabled us to collapse across each deck type and doubled our power when analyzing fMRI data from trials involving risky versus safe choices. Debriefing of subjects indicated that they were not aware that decks A and B, and C and D, were the same—many reported different subjective feelings toward the decks within each pair;
- 2) Trials resulting in a win and a loss were separated. In the original version of the task, subjects either win money or occasionally win and then immediately lose money within the same trial, but we separated these into pure win or loss trials to optimize the contrast between wins and losses. The reinforcement schedule was carefully constructed so that the variable amounts won were about double and those lost were similar to those in the original task, resulting in similar net wins and losses, for example, where in the original task a choice from deck A resulted in a win of £90 and a loss of £300 (a net loss of £210), in our version there was simply a loss of £240–£260. We “created” these numbers de novo to ensure the same net gain or loss as in the original IGT (+ or – £250 per 10 cards selected from each deck), whilst retaining reinforcements of similar value to those used in the original task;
- 3) Variable intertrial intervals of at least 3–5 s, where just a fixation cross was presented in the center of a blank screen were imposed. These periods served as an implicit baseline for fMRI analysis. At the beginning of the next trial, the cards reappeared accompanied by the command “wait” and then, after 2 s, subjects were instructed to “Pick a card”. The 2-s “wait” period alerted subjects that a decision would soon be required to ensure that they were able to make their decision with the allocated 3-s time window;
- 4) Subjects had to make their response within 3 s of the “Pick a card” prompt appearing or else they received a “Too Late” message and the task progressed to the next trial.

Trials lasted 10–12 s (mean 11 s) and the timing for each trial was as follows: Cards appear on screen and subject told to “wait” (2 s); “Pick a card” prompt is displayed under the cards and subjects must select one of the 4 decks using a 4-key button box in their right hand (up to 3 s); immediately after a response has been made the reinforcement is displayed (e.g., “You have won £X”) and the green bar moves up or down (2 s); a fixation cross is then presented in the center of the screen for a variable period (of at least 3–5 s) until the next trial begins. The duration of the fixation cross on each trial was adjusted for the subject’s reaction time, so that the task lasted exactly 1321 s (22.02 min) for each subject.

The same instructions were read to all participants. They then practiced a control task (5 trials) inside the MRI scanner prior to the scan to familiarize themselves with task requirements. The task began with 10 trials of a visuomotor control task followed by 100 trials of the experimental task, and ended with another 10 trials of the control task.

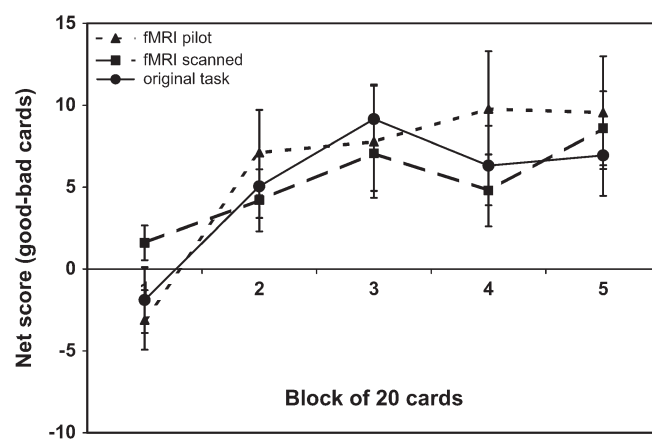
During the control task, subjects were presented with 4 decks of cards labeled E, F, G, and H and were instructed to pick a card from a specific deck by pressing one of 4 buttons using their right hand. Each trial therefore began with, for example, “Pick card E” rather than “Pick a card.” Subjects were encouraged to be accurate and were informed that a correct response would be recorded for up to 3 s after the command. As “reinforcement,” subjects saw the message “You picked a card,” displayed for 2 s after a response had been made. The green bar at the bottom of the screen did not move up or down during the control task. The decks E, F, G, and H were a different color than A, B, C, and D. The screen appearance and trial structure was otherwise identical in the control and experimental tasks.

Following task completion, participants were asked to describe any strategy they had used, and then they were asked whether they had picked more cards from any particular deck(s), or whether they had avoided any particular deck(s), and why they had done so. Responses were graded 1 if participants explained that cards from decks A (and/or B) resulted in a net loss, whereas cards from decks C (and/or) D produced a net gain and 0 if they gave another (incorrect) response. These questions aimed to determine which subjects had developed explicit awareness of the rules for winning the IGT.

Our modified version of the IGT was first tested outside the MRI environment in a separate group of 9 male subjects to ensure that the above modifications did not alter task performance relative to the original computerized version of the IGT. Results were compared with those obtained in a different group of 19 male controls who had completed the original computerized version of the IGT as part of another study (Lawrence et al. 2006). Repeated-measures ANOVA for net score  $[(C + D) - (A + B)]$  over the 5 blocks of 20 cards selections, with group as a between-subjects factor, indicated no significant differences between the 2 groups/tasks ( $F_{1,26} = 0.18$ ,  $P = 0.67$ ). There was a significant main effect of block ( $F_{4,23} = 7.5$ ,  $P < 0.001$ ), but no interaction of group  $\times$  block ( $F_{4,23} = 0.75$ ,  $P = 0.57$ ), showing that similar levels of learning were observed in both tasks (see also Fig. 1). None of the pilot subjects participated in the scanning experiment.

### Image Acquisition

Gradient echo echoplanar imaging (EPI) data were acquired on a GE Signa 1.5 T system (General Electric, Milwaukee, WI) at the Maudsley Hospital, London. 440  $T_2^*$ -weighted whole-brain volumes depicting BOLD contrast (Ogawa et al. 1990) were acquired over 22 min at each of 42 noncontiguous planes (3 mm thickness, 0.3 mm interslice gap) parallel to the intercommissural (AC-PC) line; echo time 40 ms,



**Figure 1.** Behavioral validation of the IGT modified for fMRI. Performance in healthy male controls in the original and modified version of the task. Graph shows the mean ( $\pm$ SEM) net score per block of 20 card selections in a group ( $n = 19$ ) performing the original computerized version of the task (taken from Lawrence et al. 2006; solid line, circles), a group ( $n = 9$ ) performing the modified version in a pilot experiment (dotted line, triangles), and a group ( $n = 15$ ) performing the modified version during the present fMRI experiment (dashed line, squares). There were no differences in performance between these groups.



repetition time 3 s, flip angle 90°, field of view 24 cm, 64 × 64 matrix, 3.75 × 3.75 mm in-plane resolution. This EPI dataset provided almost complete brain coverage (Simmons et al. 1999) and had sufficiently high spatial resolution to be used for conversion of subject's data into standard space (Montreal Neurological Institute [MNI] template) during analysis. Stimuli were back-projected onto a screen at the subject's feet and were viewed with the aid of prism glasses attached to the inside of the radio-frequency head-coil.

### fMRI Analyses

Data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab 6.5 (Mathworks, Inc, Natick, MA) using an event-related model (Josephs et al. 1997). EPI data were first corrected for head movements, unwarped (Andersson et al. 2001), spatially normalized (Friston et al. 1995a), and smoothed using an isotropic 8-mm full-width half-maximum Gaussian kernel to minimize noise and residual differences in gyral anatomy. Each normalized image set was also band pass filtered with a 128-s temporal high-pass filter to remove low-frequency noise. Inspection of motion correction parameters for all 15 subjects revealed that none had moved further than 2 mm or rotated more than 1.5°, enabling all data to be included in the data analysis. A multiple regression analysis was applied to the EPI data, with regressors corresponding to the trials where “risky” decisions were made (selections from decks A and B), trials where “safe” decisions were made (selections from decks C and D), and trials in the control task. Regressors consisted of trial reaction times timed from the beginning of the scan. When no card selection was made (on average < 1 (0.67)), these trials were excluded from the analysis. Each condition was modeled by convolving delta functions of relevant decision times with a canonical hemodynamic response function. Contrast images were calculated by applying linear contrasts to the parameter estimates for the regressor of each event. The contrast images were then entered into one-sample *t*-tests, to instantiate random-effects group analyses (Friston et al. 1995b). The *t*-test maps were thresholded using a voxel-wise *P* value of 0.001 (uncorrected) followed by an adjustment for minimum cluster volume (*P* < 0.05, corrected for whole-brain volume). Reported voxels correspond to standardized MNI coordinate space. Conversion to coordinates in the Talairach and Tournoux atlas (Talairach and Tournoux 1988) was also carried out using Matthew Brett's mni2tal tool (see <http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) to enable approximate labeling of cortical BAS.

A second multiple regression analysis examined responses to reinforcement. For this analysis, events were recoded as win or loss trials and 2-s long events were counted from the time of the onset of reinforcement (when the subject pressed a button to select a card).

Contrast maps were generated to examine our main hypotheses. These included

- 1) Decision-making per se. Choices from all experimental decks (A, B, C, D) versus directed responding in the control task (“general decision making”).
- 2) Choices from risky (A + B) decks versus safe (C + D) decks (“risky decision-making”).
- 3) Successful task learning: To examine whether neural activity in the above contrasts was related to task performance we used whole-brain correlations with the total net score. In addition we explored whether activation in clusters showing a significant correlation with task performance (i.e., using this as a mask) changed over time on the task, by examining linear modulation of activation in these regions. For this analysis, all decision events (choices from decks A to D) were weighted by a linear trend over the session (i.e., starting at -1, going through zero and ending with the final trial weighted as 1) and this was compared with mean activation during the control events on a subject-by-subject basis. The resulting beta value for each subject was entered into a standard one-sample *t*-test to determine (masked) regions showing a significant effect of the linear trend on the decision (ABCD) events, relative to the control task. We suggest that regions showing both a positive association with performance and a modulation over time may be related to successful learning.

- 4) Choices that resulted in wins versus losses.

Statistical analyses of behavioral data were carried out with the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS, Inc, Chicago, IL).

## Results

### Performance on the Gambling Task

Subjects performed the visuomotor control task at near ceiling levels, with all subjects choosing the deck as instructed on at least 95% of trials (mean accuracy 99%). Performance on the IGT modified for fMRI varied between participants, with total net scores ranging from -31 to +69 (mean  $26.27 \pm$  [SD] 31.53) out of a total possible range of -100 to +100. The substantial individual differences in performance aided the regression analysis of performance against the BOLD data. There was no relationship between subjects' IGT score and their mean reaction time (RT; group average;  $655.6 \pm$  [SD] 122.4 ms), and no difference in RTs for choices from risky versus safe decks, so RT data were not explored further.

Repeated-measures ANOVA was carried out with the net score per 5 blocks of 20 card selections as the repeated measures to assess learning. Results indicated a significant effect of block,  $F_{4,56} = 4.37$ ,  $P < 0.01$ , indicating that performance improved over time as expected. Within-subjects contrasts further revealed that a linear function explained the change in score over blocks ( $F_{1,14} = 8.43$ ,  $P < 0.05$ ). The majority of subjects ( $n = 9$ ; 60%) showed learning on the IGT and obtained a net score of at least 20. The remaining 40% ( $n = 6$ ) failed to show robust learning and obtained net scores of 4 and below. Debriefing of subjects indicated that 10 subjects (67%) had developed explicit awareness of the correct strategy to win the IGT, and these individuals performed significantly better (mean net score  $39.9 \pm 30$ ) than the 5 subjects who failed to develop such an awareness (mean net score  $-1 \pm 6.8$ ;  $F_{1,14} = 8.69$ ,  $P = 0.01$ ). All good performers were therefore able to report the correct strategy for winning the IGT, in addition to one poor performer.

The above distribution of performance and explicit understanding is similar to that we observed previously in 19 healthy males using the original computerized version of the IGT as part of another study (Lawrence et al. 2006). Indeed, there were no differences in overall performance between these 2 groups ( $F_{1,32} = 0.004$ ,  $P = 0.95$ ) and no differences in learning over the task (nonsignificant block × group interaction,  $F_{4,29} = 1.99$ ,  $P = 0.1$ ). In addition, the learning curve observed in this study was very similar to that reported in controls using the computerized task (with decks A'B'C'D') in Bechara et al. (2000). This second behavioral validation confirms that our version of the IGT adapted for event-related fMRI results in similar levels of performance to the original computerized version. Figure 1 shows the change in score over the 100 experimental trials in the 15 male controls scanned in this study, the 9 male controls in the pilot study and the 19 male controls from our previous study performing the original computerized version of the IGT.

### BOLD Activity during Decision Making versus Control Task and Relationship to Task Performance

Comparison of BOLD activity during card selection in the decision-making versus control task revealed only one cluster,

in the VM PFC that showed significantly more activation in the decision-making condition (Table 1). This cluster was located bilaterally in the medial OFC (BA 11)/ventral anterior cingulate cortex (BA 24/32), extending into the caudate (see Fig. 2, green cluster).

We used a whole-brain correlation with the total net score to examine whether activation during decision-making per se was related to IGT performance. Activation in one small cluster showed a significant positive correlation with net score; this was located in the precentral gyrus, BA 6/4 (Table 1), just dorsolateral to the similar cluster identified in the risky versus safe correlation analysis described below.

**Table 1**

Brain regions from the active decision-making versus control task contrast showing significant activation and a significant relationship with task performance

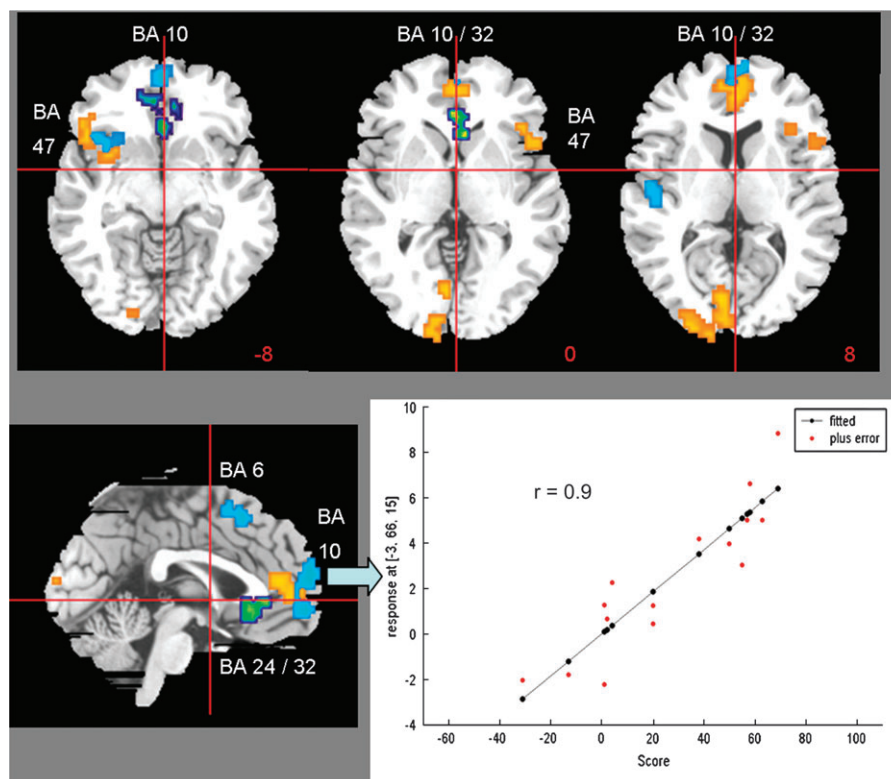
Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)	Voxel (Z-value)
<b>Decision making per se</b>					
Anterior cingulate/medial OFC	R	24/32/11	120	9, 36, -3	3.90
Caudate	R			6, 21, 0	3.82
Anterior cingulate	L	24		-3, 36, -3	3.69
Precentral gyrus	L	6/4	29	-63, -9, 30	4.46
				-63, -6, 21	5.53

Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI) and coordinates in italics refer to 2 local maxima more than 8 mm apart, in mm (MNI). BA estimated from mni2tal conversion to Talairach and Tournoux (1988) with positive = right (x), anterior (y), and superior (z).

### **BOLD Activity during Choices from Risky versus Safe Decks and Relationship to Task Performance**

The contrast of choices from risky (A + B) versus safe (C + D) decks revealed greater medial frontal gyrus activation during risky decisions, albeit in a more dorsal cluster (BA 24/32/10/9) relative to that reported above for decision-making per se. Choosing cards from risky decks was also associated with increased activation in lateral OFC (BA 47), extending into the insula, bilaterally, and in the visual (occipital) cortex (Table 2, Fig. 2, orange clusters). There were no regions showing significantly greater activation to choices from safe relative to risky decks.

We examined whether neural activity in the key contrast of choices from risky versus safe decks was related to task performance using a whole-brain correlation with the total net score. This analysis revealed 4 clusters showing a significant positive correlation with performance (Table 2, Fig. 2, blue clusters). The most significant correlated cluster ( $r = 0.902$ ) was located in the medial frontal gyrus, BA 10, in a region anterior to, but overlapping with, the medial frontal gyrus cluster identified in the main risky versus safe contrast detailed above. Activity in another region identified in the main contrast, the left lateral OFC (BA 47), was also significantly related to task performance ( $r = 0.82$ , see overlapping blue and orange clusters, Fig. 2). Finally, activity in more posterior frontal regions, the pre-supplementary motor area (pre-SMA) (BA 6/8) and lateral sulcus (secondary somatosensory cortex, SII), was positively correlated with task performance ( $r = 0.86$  and  $r = 0.84$ , respectively).



**Figure 2.** BOLD activity during the IGT. Clusters showing significant activation during decision-making versus the control task (green) and during choices from risky versus safe decks (orange). Regions in the risky versus safe contrast showing a positive correlation with task performance are shown in light blue. Activations are displayed on axial sections starting at  $z = -8$  (top row), and a midline sagittal section (bottom) in neurological orientation (left is left). Graph shows the correlation between net score on the IGT and activation in BA 10 (coordinates  $-3, 66, 15$ ). Actual neural responses in the 15 participants are represented by red points and idealized responses on a line of best fit are shown in black.

**Table 2**

Brain regions showing significant activation during choices from risky (A, B) versus safe (C, D) decks and showing a correlation with task performance

Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)	Voxel (Z-value)
<b>Choices from risky versus safe decks</b>					
Middle/superior occipital cortex	L	19	176	−30, −93, 12	4.53
Anterior cingulate gyrus/	L/R	32	142	−3, 42, 12	4.19
				−3, 51, 3	4.02
Superior medial frontal cortex		10/9		−9, 48, 18	3.70
Inferior OFC	L	47	39	−48, 21, −9	3.98
Inferior OFC/	L	47	41	−27, 21, −18	3.87
Insula	L			−36, 6, −6	3.80
	L			−30, 12, −12	3.48
Inferior frontal operculum	R	47	40	51, 18, 3	3.83
Insula	R			36, 27, 3	3.42
<b>Positive correlation with score</b>					
Superior medial frontal gyrus/	L/R	10	96	−3, 66, 15	4.60
				6, 66, 9	4.17
Medial OFC				0, 60, −6	4.08
Pre-SMA	L	6/8	74	−3, 21, 51	4.14
				−6, 9, 60	3.89
				−6, 18, 66	3.82
Lateral sulcus (SII)	L		31	−54, −9, 9	3.89
	L	47	32	−42, 21, −9	3.75
Inferior OFC/insula				−36, 15, −6	3.67
<b>Decreases in activation over time (linear)</b>					
Inferior OFC/insula	L	47	12	−27, 21, −6	3.87
In good performers only ( $n = 9$ )				−42, 15, −3	3.56
Pre-SMA	L	6/8	11	−3, 21, 51	3.76

Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI) and coordinates in italics refer to 2 local maxima more than 8 mm apart, in mm (MNI). BA estimated from mni2tal conversion to Talairach and Tournoux (1988) with positive = right (x), anterior (y), and superior (z).

Finally, we examined which clusters of performance-related activation varied over time. Our behavioral data indicated that performance showed a linear change (improvement) over time so we explored linear increases and decreases in task-related activity (relative to the control task) within performance-correlated areas. No regions showed a linear increase in activation over time. However, activation in part of the left lateral OFC (BA 47)/ insula cluster showed a linear decrease in activation across all 15 participants (Table 2, Fig. 2, blue left BA 47 cluster). When only the 9 participants who had shown robust learning (total score  $\geq 20$ ) were examined, part of the pre-SMA (BA 6/8) cluster that correlated with performance showed a linear decrease in activation over time (Table 2).

### **BOLD Activity during Wins versus Losses in the Gambling Task**

Comparison of BOLD responses during all periods of wins versus losses (independent of deck chosen) revealed a large network of brain regions responding more to wins (Table 3, Fig. 3). Clusters were located in traditional reward-related brain areas in the ventral striatum and thalamus, along with activation in posterior parieto-occipital regions related to visual attention. In addition, win-related activity was observed in the cerebellum and supplementary motor cortex (BA 6). There were no significant increases in response to losses relative to wins.

### **Discussion**

This study disentangles, for the first time, the contributions of different PFC regions to performance of a modified version of the IGT. The findings support a key role for the medial frontal gyrus, BA 10, in risky decision-making and successful task performance, providing a powerful replication of the one previous fMRI study of decision-making in the IGT (Fukui et al. 2005). Further contrasts suggest equally important roles for the

left lateral OFC (BA 47) and dorsal (pre-supplementary motor) cortex in learning to win on the task, whereas pointing to a more general (performance-unrelated) role for the ventro-medial OFC. These findings help to reconcile inconsistencies from neuropsychological studies concerning the role of these ventral and dorsal prefrontal brain areas in the IGT (e.g., Bechara et al. 1994, 1999; Tranel et al. 2002 vs. Manes et al. 2002; Clark et al. 2003; Fellows and Farah 2005), inform the results of PET studies of this task, and are consistent with recent frameworks describing neural networks underlying decision-making (Bechara and Damasio 2005; Ernst and Paulus 2005).

We predicted that decision-making in the context of risk, that is, task performance per se, would be associated with VM PFC and ventrolateral PFC activity, in addition to several other regions. Our contrast of active decision-making versus the control task, however, only revealed activity in one large VM PFC cluster encompassing the bilateral subgenual anterior cingulate (BA 24/32) and the medial OFC (BA 11). Activation in this region was predicted from neuropsychological and PET studies of the IGT (Bechara et al. 1994, 1999; Ernst et al. 2002; Bolla et al. 2003, 2004). In our study, VM PFC activation is likely to have been related to more general task components such as the monitoring of rewards and response-reinforcement contingencies across trials (Elliott et al. 1999; O'Doherty et al. 2001; Kringelbach and Rolls 2004; Rogers et al. 2004; Windmann et al. 2006), as there was no reinforcement in the control task. It is interesting to note that the VM PFC activation observed here for task performance per se borders onto both the more rostro-dorsal medial frontal gyrus activation related to risky versus safe decisions and the more ventro-caudal right caudate activation related to processing of wins versus losses (see below and also Rogers et al. 2004). Taken together, these findings suggest that the role of this VM PFC cluster is to integrate information from the processing of rewards to guide decisions; perhaps by transferring relevant reinforcement-related information to the

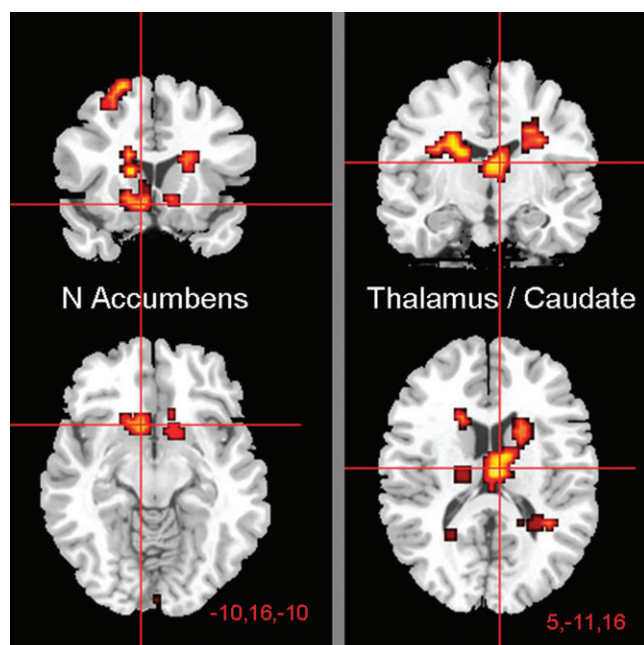


**Table 3**

Brain regions showing significant activation in response to wins versus losses (all decks)

Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)	Voxel (Z-value)
Precuneus/angular gyrus	R	30	374	24, -48, 21	4.78
Thalamus	R		125	3, -12, 15	4.58
Cerebellum	R		349	36, -75, -45	4.58
Caudate/insula	L		201	-21, -21, 27	4.47
Caudate (includes nucleus accumbens)	L		109	-18, 18, 12	4.32
Cerebellum	R		106	12, -42, -48	4.32
Cuneus/parieto-occipital sulcus	L	23/30	44	-24, -48, 24	4.14
Caudate	R		127	27, -12, 30	4.11
Inferior Parietal lobe	R	40	51	54, -39, 51	4.07
Cerebellum	L		65	-27, -63, -42	4.03
Superior frontal gyrus	L	6	59	-21, 18, 63	3.98
Caudate/anterior cingulate	R	24	48	18, 30, 3	3.82
Superior parietal/middle occipital cortex	L	7	90	-27, -63, 54	3.69

Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI). We have omitted the 2 local maxima for the sake of brevity; these data are available on request. BA estimated from mni2tal conversion to Talairach and Tournoux (1988) with positive = right (x), anterior (y), and superior (z).



**Figure 3.** BOLD activity during wins versus losses (all decks). Activations are displayed on coronal (top) and axial (bottom) sections in neurological orientation (left is left). Cross-hairs are centered on the nucleus accumbens and thalamus/caudate, rather than on cluster peak coordinates (which are respectively, -18, 18, 12, and 3, -12, 15).

more dorsal BA 10 cluster that is specifically related to risky decision-making and successful task performance (see below). This suggested role for the VM PFC fits well with its demonstrated role in integrating reward-related autonomic input (Critchley et al. 2000), and its functional connectivity with dorsomedial PFC during high-risk decisions (Cohen et al. 2005).

Selection of cards from risky versus safe decks yielded activation in a large cluster of medial frontal gyrus, stretching from the (pregenual) anterior cingulate gyrus (BA 24/32) to the superior frontal cortex (BA 10/9). This region is anterior and dorsal to the VM PFC cluster described above and overlaps with the slightly more dorsal region (coordinates -2, 57, 21) identified using a similar contrast in the study by Fukui et al. (2005). Activation in the more anterior portion of this cluster was also strongly positively correlated with task performance

in both this and the Fukui et al. study (Fukui et al. 2005), suggesting that it plays a key role in successful IGT performance. Furthermore, activation in this same anterior BA10 region (coordinates 4, 54, 4 and 16, 66, 8) during affective judgments of emotional pictures was positively related to IGT performance (Northoff et al. 2006). We found no evidence for a linear decrease in activation over time in this region, further replicating previous findings (Fukui et al. 2005), and suggesting that BA 10 is recruited during risky decisions throughout the task. In fact, activation in this region may be associated with the development of anticipatory arousal during risky decisions (Critchley et al. 2000), which builds throughout the task and is believed to be important for learning to avoid the risky decks (Bechara et al. 1997). Studies of neurological patients suggest that lesions in both ventral and/or dorsal medial PFC result in fairly specific neuropsychological impairments affecting IGT performance (Bechara et al. 1998; Manes et al. 2002). We suggest that this anterior medial frontal gyrus (BA 10) cluster is crucial for IGT performance and that previous neuropsychological data are consistent if one assumes that lesions showed overlap within this functional region (Bechara et al. 1998; Manes et al. 2002). Recent accounts of the role of medial BA10 in general cognition suggest that it operates as a “gateway,” maximizing attention to environmental stimuli (as opposed to self-generated, stimulus-independent thought) in the pursuit of goals in “ill-structured” tasks (Burgess et al. 2007). Others suggest that this region is implicated in making decisions about emotional material in the context of goal-directed behavior, that depend upon affective (as opposed to cognitive) evaluation of that material (Rogers et al. 2004; Northoff et al. 2006). Such affective evaluation requires directing attention to stimulus-related internal states, which are putatively represented by autonomic signals or “somatic markers” (Bechara and Damasio 2005). In the context of the IGT, BA 10 activation is associated with using internal signals (generated by external cues/reinforcements and communicated via the ventromedial and lateral OFC) to select goal-directed responses.

Another key region identified by the risky versus safe decision contrast was the bilateral ventrolateral PFC/lateral OFC (BA 47), extending into the insula. Moreover, activation in the left lateral OFC was positively associated with task performance and showed a linear decrease in activation over time across the whole group. These findings suggest that the lateral OFC may play an important role early on in task performance, during the learning phase (particularly in those

who perform well), but then shows habituation in all participants as the task progresses. The lateral OFC and ventrolateral PFC have repeatedly been implicated in learning tasks involving reinforcement, particularly punishment or unsteady outcome processing (Windmann et al. 2006), and in particular, appear to underlie error-dependent response switching in reversal-learning tasks (Cools et al. 2002; Kringelbach and Rolls 2004). This cognitive function is crucial in the early stages of the IGT, when the initially high-gain decks A and B begin to lose large sums of money and participants must learn to shift their choices to decks C and D. Indeed, IGT deficits in patients with predominantly left OFC damage have been related to a reversal-learning impairment (Fellows and Farah 2005).

Related (more dorso-caudal) activations to risky versus safe decisions in the bilateral anterior insula were most likely associated with risk-tasking/anticipation of punishment in our study. fMRI studies support the role of the insula in representing negative somatic states, including those associated with risk-taking and punishment, and further reveal that insula activation is associated with subsequent behavior modification (Paulus et al. 2003; Wrase et al. 2007). Furthermore, anterior insula activation is related to explicit awareness of interoceptive signals (Critchley et al. 2004), supporting the idea that it plays a key role in the generation/processing of somatic markers, which are believed to be important for successful IGT performance (Bechara et al. 1999). In our study, activation in the left anterior insula and functionally related secondary somatosensory cortex (SII) was positively associated with task performance, reinforcing this idea. Connected activation peaks in the left lateral OFC and insula that are related to successful task performance and diminish over time, reflect the related roles of these brain regions in the IGT; the insula signaling the anticipation and receipt of larger losses during risky decisions and the lateral OFC translating this signal into response shifting, particularly during the early stages of the task.

Whilst IGT performance is particularly sensitive to VM PFC dysfunction (Bechara et al. 1994, 1998; Cavallaro et al. 2003), neuropsychological and PET studies indicate some dependence on working memory functions associated with more dorsal sectors of the PFC (Ernst et al. 2002; Manes et al. 2002; Clark et al. 2003; Bechara, 2004; Fellows and Farah 2005). In agreement with a previous PET study (Bolla et al. 2004), we did not find any specific task-related activation in the dorsolateral PFC in the current male sample, arguably because our contrasted conditions were matched in terms of their working memory demands, but we did find that activations in lateral and medial motor-related areas (precentral gyrus and pre-SMA, respectively) were positively related to task performance. Interestingly, activation in the pre-SMA, BA 6/8, also showed a linear decrease over time in our sub-set of good performers. These data suggest that, similar to the ventrolateral PFC, the pre-SMA may be recruited early on in task performance during the learning phase of the task. Indeed, activation in BA 6/8, in addition to the ventrolateral PFC, is observed during reversal learning (Cools et al. 2002). The pre-SMA is involved in planning motor responses under internal control in more complex tasks (Vorobiev et al. 1998), and activation in BA 8/6 is associated with uncertainty and decision conflict (Ullsperger and von Cramon 2003; Volz et al. 2005). Our data may therefore indicate that participants who show a greater sensitivity to uncertainty early on in the task and

respond with more careful planning of motor responses—especially during risky trials—learn the winning strategy more effectively. As explicit awareness of task strategy develops (as it did in all our good performers) and uncertainty diminishes, there is a corresponding decrease in activation in BA 6/8 in these good performers. In contrast, activation in the more ventro-anterior cluster in BA 10/32 is maintained during risky decisions throughout the task, supporting the idea that BA 32 mediates response conflict in well-defined tasks where rules are known (Volz et al. 2005).

Neural responses in regions associated with visual attention (in occipital, temporal and parietal cortices) were greater during risky decisions and in response to wins versus losses. These findings reflect predictable increases in visual attention to the more salient/arousing aspects of the task (Critchley et al. 2000); that is, participants showed heightened attention during choices from the risky decks with their larger reinforcements and in response to wins generally. There were no clusters in visual attention areas that showed a positive correlation with task performance, indicating that differences in performance were not related to varying levels of attention paid by participants. This reinforces data from neuropsychological studies showing no relationship between IGT performance and measures of attention (Clark et al. 2001; Bechara et al. 2002).

Finally, in addition to the above, we observed greater brain responses to wins than losses in several brain regions typically associated with the processing and anticipation of rewards, including the ventral striatum, thalamus, cerebellum and superior frontal gyrus (Breiter et al. 2001; Knutson et al. 2001; Rogers et al. 2004; Windmann et al. 2006). Importantly, these clusters did not overlap with those identified in the various decision-making contrasts described above, suggesting that the above activations are related to aspects of risky decision-making, rather than to processing the different levels of reward from the risky versus safe decks. These findings are similar to those of Rogers et al. (2004), showing largely separable activations in the pregenual versus subcallosal anterior cingulate cortex for the processing of reward-related information in, respectively, decision versus outcome phases of a gambling task. We did not find any regions showing greater activation to losses than wins in our modified version of the IGT. However, as BOLD responses to punishment can be manifested as deactivations in reward-related regions (Delgado et al. 2000; Breiter et al. 2001) we examined our win > loss clusters for evidence of this. Consistent with previous studies, there was significant loss-related deactivation (relative to a fixation cross baseline) in the left ventral striatum, suggesting that deactivation to loss outcomes was driving some of the wins versus loss activation in this region (data available on request).

### Limitations

Due to reported sex differences in IGT performance and brain activation, the current study examined men only. Future studies should examine whether the neural basis of advantageous decision-making as revealed by fMRI is similar in women. We did not compare fMRI data between participants who had and had not developed explicit awareness of the rules for winning in the IGT due to the small and inhomogeneous sample sizes obtained ( $n = 10$  and  $5$ , respectively). This would be an interesting question to address in future fMRI studies carried out in a larger sample. We were unable to obtain good quality skin conductance data in this study so could not



directly examine the relationship between regional brain activation, somatic signals and performance. Further fMRI studies involving careful online measurement of autonomic arousal during performance of the present task would clarify the relationship between these variables.

In conclusion and consistent with recent theoretical accounts (Bechara and Damasio 2005; Ernst and Paulus 2005), decision-making in the IGT requires the rostral medial PFC (BA 10), which is believed to integrate information from neural systems involved in executive functions (dorsolateral PFC) and outcome processing (insula, SII, medial and lateral OFC, ventral striatum) in order to affectively evaluate stimuli. Feedback from the medial OFC tracks reward value and may maintain an advantageous strategy, whereas lateral OFC/insula activation increases when reinforcements are inconsistent and the subject needs to suppress the previously rewarded response and change strategy (Windmann et al. 2006). The affective evaluation carried out by BA 10 involves both the generation of expectancy and the assessment of feedback, and leads to the selection and implementation of a motor response, which is associated with pre-SMA activation. Deciding advantageously under initially ambiguous conditions may require an adequate interplay of these continuous and dynamic processes.

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Address correspondence to Dr Natalia Lawrence, Wales Institute of Cognitive Neuroscience, School of Psychology, Tower Building, Cardiff University, Park Place, Cardiff CF10 3AT, UK. Email: LawrenceNS@cardiff.ac.uk.

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