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# The impact of prior risk experiences on subsequent risky decision-making: The role of the insula

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ABSTRACT

Risky decision-making is significantly affected by homeostatic states associated with different prior risk experiences, yet the neural mechanisms have not been well understood. Using functional MRI, we examined how gambling decisions and their underlying neural responses were modulated by prior risk experiences, with a focus on the insular cortex since it has been implicated in interoception, emotion and risky decision-making. Fourteen healthy young participants were scanned while performing a gambling task that was designed to simulate daily-life risk taking. Prior risk experience was manipulated by presenting participants with gambles that they were very likely to accept or gambles that they were unlikely to accept. A probe gamble, which was sensitive to individual's risk preference, was presented to examine the effect of prior risk experiences (Risk vs. Norisk) on subsequent risky decisions. Compared to passing on a gamble (Norisk), taking a gamble, especially winning a gamble (Riskwin), was associated with significantly stronger activation in the insular and dorsal medial prefrontal cortices. Decision making after Norisk was more risky and more likely to recruit activation of the insular and anterior cingulate cortices. This insular activity during decision making predicted the extent of risky decisions both within- and across-subjects, and was also correlated with an individual's personality trait of urgency. These findings suggest that the insula plays an important role in activating representations of homeostatic states associated with the experience of risk, which in turn exerts an influence on subsequent decisions.



## Introduction

Cumulative evidence has suggested that risky decision-making not only involves cognitive evaluation of reward and risk, but is also modulated by homeostatic signals (Loewenstein et al., 2001; Paulus, 2007). For example, risky decision-making, such as gambling, engenders strong subjective excitement or arousal (Boyd, 1976), which is associated with strong physiological changes in heart rate, blood pressure, electromyogram, cortisol level, skin temperature, and skin conductance response (see Goudriaan et al., 2004 for review). Some form of arousal or excitement is a strong reinforcer of gambling behavior (Anderson and Brown, 1984), and the size of the observed interoceptive increase can explain both normal/regular and pathological gambling (Brown, 1986; Sharpe et al., 1995). Higher arousal is associated with greater persistence (Dickerson and Adcock, 1987) and more withdrawal symptoms when trying to abstain (Wray and Dickerson, 1981).

Convergent evidence from electrophysiology, neuroanatomy, and clinical studies has ascribed a role for the insula in providing interoceptive signals, including those related to pain, temperature, taste and visceral sensation (Craig, 2002, 2003). On that basis, it has been suggested that the insula contains the fundamental substrates for human awareness of homeostatic states (Craig, 2009). By working together with other brain regions, the insula can trigger bodily states, map bodily states, and represent the relationship between changes in the bodily states and the objects that elicited them (Bechara and Damasio, 2005). The insular cortex contains Von Economo neurons (VENs) that are abundant with Dopamine D3 and Serotonin 2b receptors, and thus is especially suitable to make fast decisions regarding reward and punishment by integrating the "gut feelings" from the visceral organs (Allman et al., 2005). Mounting evidence has suggested that the insula plays an important role in signaling the awareness of the urge for drug addictions (Naqvi and Bechara, 2009).

These findings lead to the hypothesis that the insula is a key region that integrates interoceptive (i.e., bodily) states into conscious feelings that may be subjectively perceived as an urge. In the case of cigarette smoking, for example, such interoceptive signals mediated through the insula can interfere with the decision-making processes

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that help people resist the urge to smoke (Naqvi and Bechara, 2009). Consistently, the insula is also involved in other types of biological urges, including drug usage (Brody et al., 2002; Garavan et al., 2000; also see Naqvi and Bechara, 2009 for review; Pelchat et al., 2004; Wexler et al., 2001), excessive food consumption (Pelchat et al., 2004), and eye blinking (Lerner et al., 2009).

Considering that both drug use (Naqvi and Bechara, 2009) and gambling (Anderson and Brown, 1984) involve strong interoceptive responses, and that pathological gambling resembles drug addiction in several core respects (Potenza, 2006; Shaffer et al., 2004), one would expect that the insula is also involved in risky decision-making. Indeed, many neuroeconomic studies guided by economic models have found insular activation when subjects make risky decisions involving gains and losses and have implicated the insula in computing different decision parameters, such as monetary losses (Paulus et al., 2003), gains (Izuma et al., 2008) or both (Clark et al., 2009; Elliott et al., 2000), and decision uncertainties (e.g., risk) (Critchley et al., 2001; Preuschoff et al., 2008), as well as risk prediction-errors (Preuschoff et al., 2008). The question we aimed at addressing in the present study is whether the creation of an urge to make a bet or gamble would also engage mechanisms mediated through the insula, which can play a role in influencing decision-making processes that involve risks and rewards.

In the present study, we used functional magnetic resonance imaging (fMRI) and a simple gambling task simulating risky decision-making. By presenting subjects with gambles that they would be very likely to accept or gambles that they would be very likely to reject, we could manipulate the prior risk experiences and neural responses in regions representing homeostatic states, such as the insula. Probe gambles were then used to examine how prior risk experiences would affect their subsequent risky decision-making and the underlying neural mechanisms. Subjects' personal trait of urgency was also measured and correlated with their risk behaviors and insular activation, since this scale has been shown to be predictive of many addictive behaviors, including alcohol abuse (Fischer and Smith, 2008; Whiteside and Lynam, 2003), tobacco craving (Billieux et al., 2007), pathological gambling (Fischer and Smith, 2008), and compulsive buying (Billieux et al., 2008).

## Materials and methods

### *Subjects*

Fourteen healthy adults participated in this study (7 males and 7 females, mean age of 23.8 years, ranging from 22 to 29). All subjects had normal or corrected-to-normal vision. They were free of neurological or psychiatric history and gave informed consent to the experimental procedure, which was approved by the University of Southern California Institutional Review Board.

### *The modified cups task*

Fig. 1A depicts the Modified Cups Task (Levin et al., 2007) and the experimental design. In each gamble, a number of cups (ranging from 3 to 11) were presented on the computer screen, with the first cup containing a large gain (ranging from $4 to $8) and each of the rest containing a small loss ($1). The number of cups thus served as a simple cue for the probability of winning. Participants were asked to decide whether they would take the gamble or not. If they took a gamble, they could either win or lose the gamble, as determined by the computer following a random process (see exceptions described below). If they passed on the gamble, they would win or lose nothing. The probability and magnitude of the gain were independently manipulated such that some combinations of probability and magnitude created a fair gamble (FG), that is, the expected value (EV) of the gamble equals zero (e.g., $6 gain in one cup and $1 loss in all the other 6 cups) (Fig. 1A). Some combinations are risk-advantageous (RA), meaning that the EV is larger than zero (e.g., $6 gain in one cup

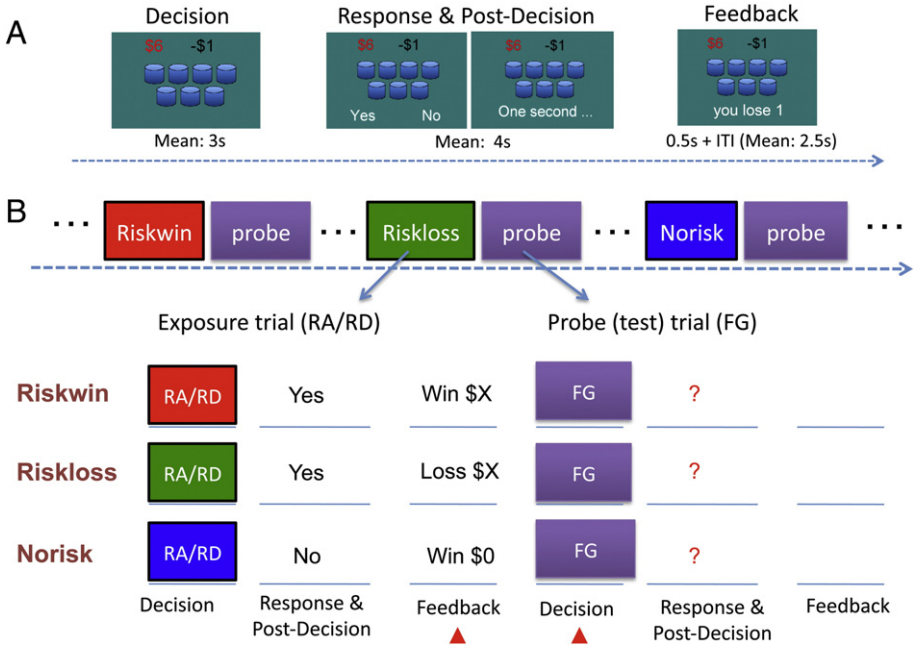


**Fig. 1.** (A) The structure of the gambling task and (B) the experimental design. In each gamble, a number of cups were presented to the participants with the first one containing a large gain and all the others containing a small loss. At the Decision stage, participants were shown the gamble and were asked to decide whether or not to take the gamble. They were not able to make any button response until after a varied period of delay, the response cue ("Yes" and "No" on each side, varied across trials) was shown. After the response, a 0.5-s feedback was presented after varied period of delay to inform participants of the outcome. The next trial began after a jittered delay. Depending on the combination of the reward amplitude and probability (the number of cups), the gamble could be fair gamble (FG), risk advantageous (RA) or risk disadvantageous (RD). The RA and RD trials were used as the prior experience trials, each of which was followed by a FG trial serving as the probe trial to examine the effect of prior risk experiences on subsequent decisions. Based on participants' decision and outcome, there were three prior experience conditions, i.e., winning a gamble (Riskwin), losing a gamble (Riskloss) and passing on a gamble (Norisk).

and $1 loss in all the other 4 cups), whereas other combinations are risk-disadvantageous (RD), meaning that the EV is less than zero (e.g., $6 gain in one cup and $1 loss in all the other 7 cups).

Each trial was divided into three stages, i.e., a Decision stage, a Response and Post-Decision stage, and a Feedback stage (Fig. 1A). At the Decision stage, participants were shown the gamble and were asked to think about the gamble before making any response. After a varied period of delay (mean 3 s, ranged from 1.5 to 5 s as drawn from an exponential distribution), the response options "Yes" and "No" were shown on the screen and participants were asked to indicate their response by a button press within 3 s, otherwise they would lose $1. The position of the response cue varied from trial to trial so that participants were not able to predict its position and plan any motor response at the decision stage. After the response and a delay ranging from 2.5 to 6 s (mean = 4 s), feedback to inform participants of the outcome was presented for a period of 0.5 s. The next trial would begin after a jittered delay (mean 2.5 s, ranged from 1 to 4.5 s). An in-house program was used to optimize the design to make sure we could effectively separate the neural responses associated with each decision stage (Christakou et al., 2009; Rogers et al., 2004).

### *The experimental design*

The primary goal of this study was to examine how individuals' gambling decisions were modulated by their prior risk experiences. Rather than arranging the trials randomly and then categorizing them post hoc based on participants' choices and outcomes, the present study used a different approach to enable better control of the decision context, and to minimize the requirement for trial matching. In doing so, we included two types of trials in this experiment: prior experience trials and probe trials (Fig. 1B). The prior experience trials can be further categorized into three types: risk and win (Riskwin), risk and lose (Riskloss), and no risk (Norisk). Following each prior experience trial, a probe trial was presented to examine how prior experience affected subsequent decisions. Our previous study had shown that participants tended to take a risk on most of the RA trials and seldom take a risk on the RD trials, whereas the risk rate on the FG trials varied significantly across participants (Xue et al., 2009). Accordingly, RA and RD trials were selected as prior experience trials to allow more control of the decision context. FG trials, which served as probe trials to provide a sensitive measure of the prior experience effect, were then presented after each of the prior experience trials. Critically, the number of RA trials was twice the number of RD trials, with half predetermined as win trials and half as loss trials if participants chose to gamble on those trials. They would receive no gain or loss if they chose not to gamble. Although the final categorization of the prior experience trials was still based on subjects' actual decisions and outcomes, this manipulation allowed us to obtain roughly equal numbers of win and loss trials in each condition. Also, this manipulation allowed us to match the probe trials following each prior experience condition on the following decision parameters: expected value, risk (defined as reward variance), reward probability and reward amplitude. Although this slightly increased the probability of gain in the RA trials, it did not significantly change the win probability for the task as a whole. Post-study debriefing indicated that participants did not notice this manipulation, nor did they change their gambling strategies accordingly. Since the structure of the prior experience trials and the probe trials were identical and participants were simply told to decide whether or not to take each gamble, participants were not aware of the purpose of the present study.

### *Urgency measurement*

The urgency trait was assessed using the urgency subscale of the UPPS Impulsive Behavior Scale (Whiteside and Lynam, 2001). We concentrated on this scale because it measures an individual's tendency to give in to strong impulses such as cravings akin to the addictive behaviors of interest here (e.g., "I have a problem resisting my cravings (for food, cigarettes, etc.) "). Each of the 12 items on the scale was scored from 1 (I agree strongly) to 4 (I disagree strongly).

### *MRI procedure*

Subjects lay supine on the scanner bed, and viewed visual stimuli back-projected onto a screen through a mirror attached onto the head coil. Foam pads were used to minimize head motion. Stimulus presentation and timing of all stimuli and response events were achieved using Matlab (Mathworks) and Psychtoolbox (www.psychtoolbox.org) on an IBM-compatible PC. Participants' responses were collected online using a MRI-compatible button box. Event-related design was used in this study. To separate the neural responses associated with making a decision from those associated with feedback processing, random jitters were added between each stage and the sequence was optimized for design efficiency (Dale, 1999) using an in-house program. In total, each run included 72 trials and lasted 12 minutes. Participants finished two runs of the gambling task. In order to avoid the wealth effect, they were told in advance that their final payoff would be randomly chosen (by flipping a coin) from one of the two runs.

### *MRI data acquisition*

fMRI imaging was conducted in a 3T Siemens MAGNETOM Tim/Trio scanner in the Dana and David Dornsife Cognitive Neuroscience Imaging Center at the University of Southern California. Functional scanning used a z-shim gradient echo EPI sequence with PACE (prospective acquisition correction). This specific sequence is designed to reduce signal loss in the prefrontal and orbitofrontal areas. The PACE option can help to reduce the impact of head motion during data acquisition. The parameters are: TR = 2000 ms; TE = 25 ms; flip angle = 90°; 64 × 64 matrix size with resolution 3 × 3 $mm^2$. Thirty-one 3.5-mm axial slices were used to cover the whole cerebral and most of the cerebellum with no gap. The slices were tilted about 30 degree clockwise from the AC–PC plane to obtain better signals in the orbitofrontal cortex. The anatomical T1-weighted structural scan was done using an MPRAGE sequence (TI = 800 ms; TR = 2530 ms; TE = 3.1 ms; flip angle 10; 208 sagittal slices; 256 × 256 matrix size with spatial resolution as 1 × 1 × 1 $mm^3$).

### *Image preprocessing and statistical analysis*

Image preprocessing and statistical analysis were carried out using FEAT (FMRI Expert Analysis Tool) version 5.98, part of the FSL (FMRIB software library, version 4.1, www.fmrib.ox.ac.uk/fsl). The first four volumes before the task were automatically discarded by the scanner to allow for T1 equilibrium. The remaining images were then realigned to compensate for small residual head movements that were not captured by the PACE sequence (Jenkinson and Smith, 2001). Translational movement parameters never exceeded 1 voxel in any direction for any subject or session. All images were denoised using MELODIC independent components analysis within FSL (Tohka et al., 2008). Data were spatially smoothed using a 5-mm full-width-half-maximum (FWHM) Gaussian kernel. The data were filtered in the temporal domain using a non-linear highpass filter with a 100-s cut-off. A three-step registration procedure was used whereby EPI images were first registered to the matched-bandwidth high-resolution scan, then to the MPRAGE structural image, and finally into the standard (MNI) space, using affine transformations (Jenkinson and Smith, 2001). Registration from MPRAGE structural image to the standard space was further refined using FNIRT nonlinear registration (Andersson et al., 2007a,b). Statistical analyses were performed in

the native image space, with the statistical maps normalized to the standard space prior to higher-level analysis.

The data were modeled at the first level using a general linear model within FSL's FILM module. In the first analysis, the following six trial types were modeled: three contextual trial types (Riskwin, Riskloss and Norisk) and their respective follow-up probe trials. Each type of trial was modeled as three distinct events associated with different decision stages: Decision, Response/post-decision, and Feedback. The event onsets were convolved with a canonical hemodynamic response function (HRF, double-gamma) to generate the regressors used in the GLM. Temporal derivatives were included as covariates of no interest to improve statistical sensitivity (Friston et al., 1998). Null events were not explicitly modeled, and therefore constituted an implicit baseline. In this paper, we were particularly interested in the feedback-related BOLD responses in the prior experience trials and the decision-related BOLD responses in the probe trials.

The second analysis was similar to the first analysis except that we broke down the decision-related BOLD response for the probe trials according to participants' subsequent decisions (Risk vs. Norisk), as well as different prior risk experiences (Riskwin vs. Riskloss vs. Norisk), which allowed us to examine whether the insular activation in the decision stage could predict subjects' choices. Four subjects made very few risky choices after at least one of the three prior risk experience conditions (see Supplementary Table 1 for their performances); thus only 10 subjects (6 male and 4 females) were included in this analysis.

A higher-level analysis created cross-run contrasts for each subject for a set of contrast images using a fixed effect model. These were then input into a random-effect model for group analysis using OLS (Ordinary Least Squares) simple mixed effect with automatic outlier detection (Woolrich, 2008). Unless otherwise noted, group images were thresholded using cluster detection statistics, with a height threshold of $z>2.0$ and a cluster probability of $p<0.05$, corrected for whole-brain multiple comparisons based on Gaussian Random Field Theory (GRFT). For analyses with specific anatomical hypotheses (i.e., activation in the insular cortex), maps were corrected using the adaptation of Gaussian Random Field Theory for small volumes, which were anatomically defined according to an anatomical atlas (Tzourio-Mazoyer et al., 2002).

We further correlated the neural activities with behavioral performance across participants. Voxelwise correlation between the neural effect of prior risky experiences (brain activation when making a decision after Norisk minus that after Riskwin) and the corresponding behavioral effect (Risk rate for a decision after Norisk minus that after Riskwin) was conducted across subjects. Voxelwise correlation was also conducted between the neural effect of prior risk experiences and an individual's personality trait of urgency. An uncorrected threshold of $p<0.001$ was used for this analysis.

### *Region-of-interest (ROI) analyses*

ROIs were created from clusters of voxels with significant activation in the voxelwise analyses. Using these regions of interest, ROI analyses were performed by extracting parameter estimates (betas) of each event type from the fitted model and averaging across all voxels in the cluster for each subject. Percent signal changes were calculated using the following formula: [contrast image / (mean of run)] × ppheight × 100%, where ppheight is the peak height of the hemodynamic response versus the baseline level of activity (Mumford, 2007). Correlations between behavioral and ROI data were based on Pearson product–moment correlations.

## Results

### *Gambling decisions were modulated by previous risk experiences*

Overall, the relatively young, healthy subjects in the present study were appropriately sensitive to changes in EV (risk rate: RA>FG>RD, $F(2,26)=70.05$, $p<0.001$). As we had expected, participants made risky choices on most of the RA trials (87%) and seldom risked on the RD trials (11%). No significant sex differences were found in the overall risk rate or in the risk rate for each type of gamble (All $p>0.25$). Of particular interest to this study, we found that participants took significantly more risks after passing on a gamble (Norisk) than after taking a gamble (regardless of win and loss; $t(13)=2.29$, $p<0.05$). More strikingly, participants' risky choices were increased by 31% after Norisk, as compared to that after Riskwin (38% vs. 29%, $t(13)=3.20$, $p=0.007$). This effect was stronger for participants with higher urgency scores as measured by the UPPS impulsivity questionnaire ($r=0.60$, $p=0.023$), but the correlation was not significant after removing one outlier ($p=0.40$).

### *The DMPFC and insula showed stronger activation after taking a risk*

First, we examined whether our manipulation of risk experience changed the neural response in the insular cortex. Focusing on the feedback processing of the prior risk experience trials, strong activation differences were found in the dorsal MPFC (MNI: 6, 36, 32; $Z=3.50$) (Hsu et al., 2005; Xue et al., 2009) and bilateral insula (left, MNI: −38, 14, −2; $Z=4.68$; right, MNI: 40, 18, −10; $Z=4.07$) between the Riskwin and Norisk conditions (Fig. 2 and Supplementary Table 2). Slightly weaker but consistent results were obtained when contrasting the fMRI responses to the gambles that participants accepted (whether won or lost) with those to the gambles that participants rejected (Riskwin + Riskloss versus Norisk; Supplementary Fig. 2 and Supplementary Table 3).

ROI analysis was conducted in brain regions exhibiting differential activation following different risk experiences. Paired sample $t$-tests indicated that in both the left and right insula, neural responses for Norisk trials were significantly lower than those for Riskwin (left insula: $t(13)=5.22$; $p<0.001$; right insula: $t(13)=4.42$; $p<0.001$) and Riskloss trials (Left insula: $t(13)=3.36$; $p<0.005$; right insula: $t(13)=2.39$; $p<0.03$). Similar results were found in the dorsal MPFC, with lower neural responses for Norisk trials than for Riskwin trials ($t(13)=3.41$; $p=0.005$ ) and Riskloss trials ($t(13)=2.11$; $p=0.055$), suggesting that prior risk experiences (regardless of the outcome) significantly affected insular and dorsal MPFC activation. We also found that the effect was stronger on Riskwin trials than on Riskloss trials (left insula: $t(13)=2.13$; $p<0.05$; right insula: $t(13)=3.69$; $p<0.002$; dorsal MPFC: $t(13)=2.53$; $p<0.015$), suggesting that the feedback-related insular activation was also affected by the outcome, which was probably driven by the relatively larger amplitude of win.

### *ACC and insula were associated with increased risk seeking decisions after Norisk*

As shown in Fig. 3, compared to decisions following Riskwin, decisions after Norisk elicited stronger activation in the bilateral insula (left: MNI: −34, 10, 8, $Z=3.98$; right: MNI: 48, 4, 2, $Z=4.10$) and the anterior cingulate cortex (MNI: −4, 20, 24, $Z=3.71$) (also see Supplementary Table 4). Very similar results were found when comparing the decision-associated neural responses after Norisk with those after taking a gamble (regardless of win or loss) (see Supplementary Fig. 3 and Supplementary Table 5). Further ROI analysis indicated that for ACC, decisions after Norisk trials elicited stronger activation than did decisions after Riskwin trials ($t(13)=5.67$; $p<0.001$) and those after Riskloss trials ($t(13)=3.03$ ; $p<0.01$), but there was no significant difference between the latter two conditions ($t(13)=1.00$; $p>0.30$). Similarly, for the left insula, decision-related neural responses after Norisk were significantly higher than those after Riskwin ($t(13)=3.52$; $p=0.004$) and after Riskloss ($t(13)=2.69$; $p=0.019$), but there was no significant difference between the latter two conditions ($t(13)=0.23$; $p=0.81$). For the right insula, decision-

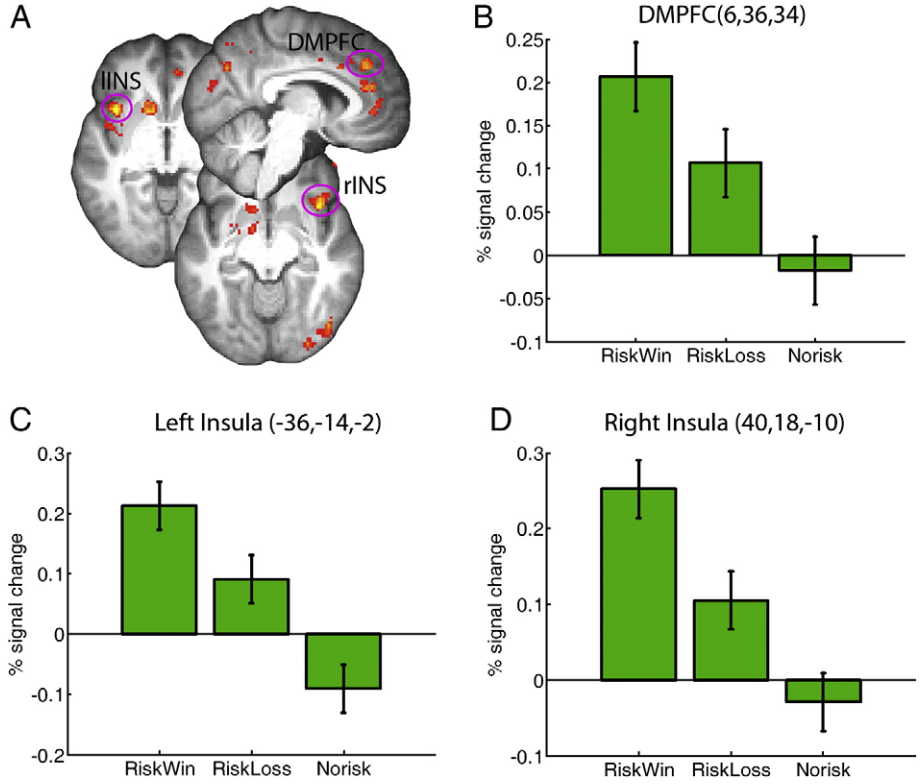


**Fig. 2.** Feedback-related activation to prior experience trials. (A) The dorsal MPFC, bilateral insula among other regions showed significantly stronger activations for Riskwin trails than for Norisk trials ($Z>2.0$, whole-brain cluster-corrected at $p<0.05$ using GRFT), which were overlain on the sagittal and axial slices of the group mean structural image. (B–D) Plots of percentage signal change for each ROI defined around the local maxima (see Supplementary Methods). Error bars denote within-subject error. See Supplementary Table 1 for a full list of foci in the comparison, and Fig. S1 for ROI results of bilateral NAcc. Also see Supplementary Fig. 2, Supplementary Table 2 for similar result when comparing taking a gambling with passing on a gamble. lINS: left insula; rINS: right insula.

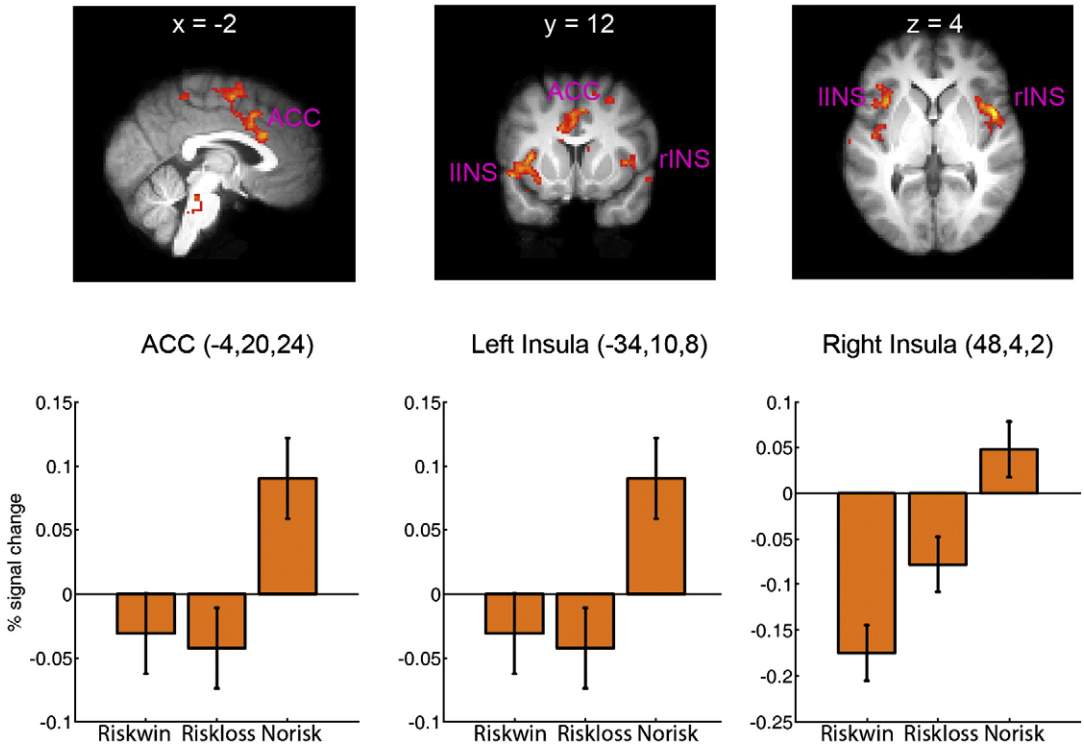


**Fig. 3.** Decision-related brain responses to probe trials following different prior risk experiences (i.e., Riskwin vs. Norisk). The anterior cingulate cortex (ACC) and bilateral insula showed stronger activity while making a decision after Norisk than after Riskwin, which was overlain on the sagittal (top left), coronal (top middle) and axial (top right) slices of the group mean structural image. All activations were thresholded using cluster detection statistics, with a height threshold of $Z>2.0$ and a cluster probability of $p<0.05$, corrected for whole-brain multiple comparisons (also see Supplementary Table 3). The bottom row shows the plots of percentage signal change for each ROI defined around the local maxima. Error bars denote within-subject error. Similar results were obtained by comparing decisions after taking a gamble with decisions after passing on a gamble (Supplementary Fig. 3, Supplementary Table 4). lINS: left insula; rINS: right insula.

related neural responses after Norisk were significantly higher than those after Riskwin ($t(13)=5.54$; $p<0.001$) and after Riskloss ($t(13)=3.13$; $p=0.008$), and there was only a marginally significant difference between the latter two conditions ($t(13)=2.04$; $p=0.06$). These results suggest that decision-related insular activation was modulated only by prior risky experiences, and not by prior outcomes.

*Right insula signaled the urge for taking a risk*

If insular activation during the decision stage indeed signals the urge that influenced the decision to take a risk, we would expect significantly stronger insular activation on trials when participants subsequently gambled than on those when they did not. This prediction was confirmed by a further analysis: the same right insular cortex (MNI: 48, 2, 0, $Z=4.00$) showing stronger activation when making decisions after Norisk than after Riskwin also showed stronger activation on trials when participants subsequently took a risk than on trials when they did not, under all three conditions (Fig. 4A). Region of interest analysis showed that there were significant main effects of prior risky experience (Riskwin vs. Riskloss vs. Norisk) ($F(2,9)=4.15$, $p=0.033$), and decision (Risk vs. Norisk) ($F(1,9)=21.76$, $p=0.001$), but the interaction was not significant ($F(2,9)=0.07$) (Fig. 4B).

Two additional analyses were conducted to further establish the connection between insular activation and the urge to take a risk. First, we correlated across participants the degree of increased insular responses during decision making after Norisk than after Riskwin and the degree of increased risky behaviors after Norisk than after Riskwin. This analysis revealed a significant positive correlation in the right insula (MNI: 34, 22, −14, $Z=4.00$) (Figs. 4C and D). That is, participants who showed more increase in risky behavior after passing on a gamble also showed more increased right insular activation in the decision making process. A similar correlation was found in the left insula (MNI: −30, 24, 2, $Z=3.50$), although at a lower significance level (Supplementary Fig. 4).

Second, we found that the right insular (MNI: 38, 22, −14, $Z=3.63$) activity increase during decision making as a result of passing on the previous gamble was also significantly correlated with individuals' personality trait of urgency: Individuals with higher urgency trait scores tended to show more insular activity increases during decision making after the insular activation was temporally reduced due to passing on a gamble (Figs. 4E and F).

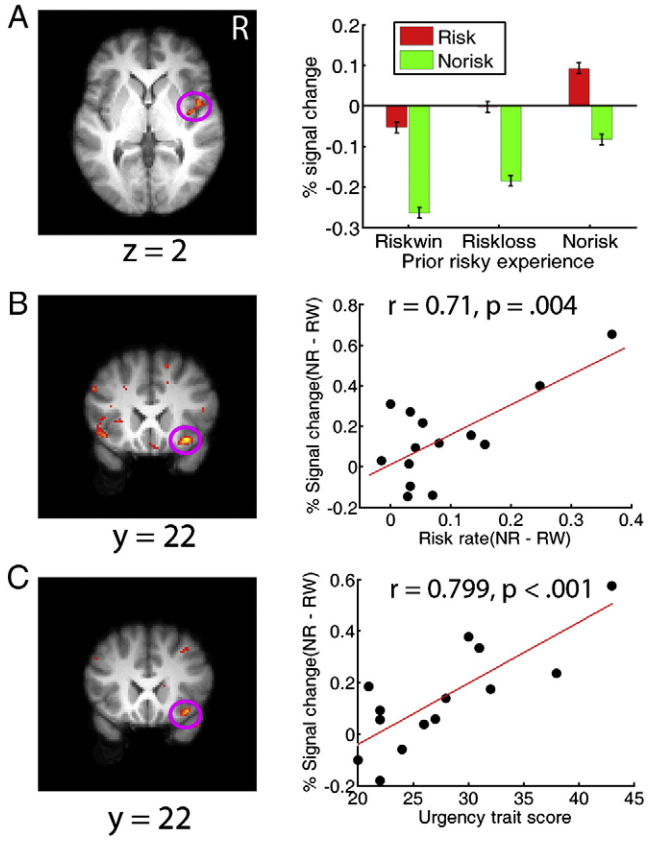


**Fig. 4.** Insular activation signals gambling urge. (A) Stronger right insular activation (MNI: 48, 2, 0, $Z=4.00$) was observed in trials participants subsequently risked than in those they did not ($n=10$). The right panel shows the plot of percentage signal change for each ROI defined around the local maxima. Error bars denote within-subject error. (B) Individuals showing more increases in risk-seeking behaviors after Norisk than after Riskwin also showed more neural activation increases in the right insula (MNI: 34, 22, −14, $Z=4.00$). A similar result was found in the left insular cortex (Fig. S4). The right panel shows the scatterplot of correlation. (C) Right insular (MNI: 38, 22, −14, $Z=3.63$) activation increases after Norisk compared to Riskwin were associated with individual urgency trait. The right panel shows the scatterplot of correlation. Clusters were considered as significant with 10 connected voxels at a height threshold of $p<0.001$; for display purpose, they were shown at $Z>2.3$. NR: decision after Norisk; RW: decision after Riskwin. It should be noted that due to small sample size and the presence of random noise in behavioral and neural measures, the correlation coefficient shown on the plots might not reflect the true effect size and the absolute value should be treated with caution.

## Discussion

The centrality of interoceptive processes in addiction and gambling has led to a theoretical model that puts the insula as the key neural structure in decision-making involving reward and risk (Naqvi and Bechara, 2009). According to this model, the insula is a region that integrates interoceptive (i.e. bodily) states into conscious feelings and into decision-making processes that involve uncertain risk and reward. Specifically, the insula represents the interoceptive effects of emotional experience associated with a decision. Exposure to the decision cue could reactivate representations of the interoceptive effects and give rise to the conscious feeling of urge. Guided by this theoretic model, the present fMRI study tested and confirmed the hypothesis that foregoing a previous gamble increased the urge for taking a subsequent risk, as mediated by the insula. These results suggest that the insula might play a key role in integrating representations of the homeostatic state associated with prior experiences and using that to guide future risky decision-making, which is a key mechanism for adaptive decision-making.

First, we found that insular activity was modulated by different risk experiences, with stronger insular activation after taking a gamble, particularly winning a gamble. This activation might reflect the homeostatic changes associated with different risk experiences. Although the present study did not directly measure the homeostatic changes and associate them with insular activity, the general role of the insula in integrating autonomic and visceral information into emotional and motivational functions has been well documented (Craig, 2002, 2003, 2009). To directly establish the association between insular activity and physiological responses, simultaneous recording of skin conductance responses and brain activity has shown that insular activity is correlated with the fluctuations over time in skin conductance responses (Critchley et al., 2000). In addition, many studies have revealed strong subjective excitement or arousal (Boyd, 1976) and physiological changes (see Goudriaan et al., 2004 for review) during risky decisions.

The emotional and interoceptive function of the insula in risky decision-making is also consistent with many neuroimaging and patient studies. For example, insular activation has been found in anticipating and experiencing both monetary loss (Paulus et al., 2003; Samanez-Larkin et al., 2008; Simmons et al., 2006) and gain (Clark et al., 2009; Delgado et al., 2000; Elliott et al., 2000; Izuma et al., 2008). Other studies have shown that the insula is also sensitive to risk level (Critchley et al., 2001; Huettel, 2006; Huettel et al., 2005; Kuhnen and Knutson, 2005; Preuschoff et al., 2006, 2008). The insula is triggered

by excessive price when deciding on whether or not to purchase a product (Knutson et al., 2007). In social decision-making, the insula is sensitive to inequity or unfairness in the distribution of a good (Hsu et al., 2008), and high insular activation will lead to the rejection of unfair offers in the ultimatum game (Sanfey et al., 2003).

More importantly, although previous studies have emphasized its role in risk avoidance, our study revealed that insular activity during decision making could also signal the urge for taking a risk. Strong insular activity was found for decisions after Norisk, where elevated risky decision making was observed. Strong insular activity was also predictive of risky decisions both within and across subjects. These findings corroborate the extensive literature showing the critical role of the insula in various types of biological urges, including drug (Brody et al., 2002; Garavan et al., 2000; also see Naqvi and Bechara, 2009 for review; Pelchat et al., 2004; Wexler et al., 2001), food (Pelchat et al., 2004) and eye blinking (Lerner et al., 2009). Furthermore, insular activation in the current study was correlated with the individual personality trait of urgency, which has also been associated with drug abuse (Fischer and Smith, 2008; Whiteside and Lynam, 2003), tobacco craving (Billieux et al., 2007), pathological gambling (Fischer and Smith, 2008), and compulsive buying (Billieux et al., 2008). Urgency is also the best predictor of severity of medical, employment, alcohol, drug, family/social, legal and psychiatric problems in individuals with substance dependence (ISD) (Verdejo-García et al., 2007). Considering the strong interoceptive response involved in both drug use (Naqvi and Bechara, 2009) and gambling (Anderson and Brown, 1984), and that pathological gambling resembles drug addiction in several core respects (Potenza, 2006; Shaffer et al., 2004), our results suggest that the insula might play a core role in many addictive behaviors (whether they involve chemical substances or not) that are related to urgency.

Third, the present study finds that the urge to gamble is modulated by prior risk experiences. Specifically, temporary deprivation of emotional arousal associated with gambling significantly increased the urge for taking a risk, a pattern that shares some key features of other addictive behaviors, although much subtler in our healthy young participants. By revealing the insular activity involved in both processing prior decision outcomes and in making subsequent decisions, our data support the hypothesized role of the insula in integrating the homeostatic state associated with prior experiences and in using that to guide future risky decision-making. Consistent with this finding, several previous studies also show that the insular response to previous decisions could predict future decisions. For example, Paulus et al. (2003) found that the insula showed stronger activation in response to punishment than in response to reward, which leads to safer subsequent choices, especially for participants prone to anxiety. In a recent study, Clark et al. (2009) found that "near-misses" trials in a slot machine game (where the chosen icon stopped one position past the payline) elicited stronger activation in the insular cortex than did the "full-misses" trials, and this activation was correlated with the subjective ratings of willingness to continue gambling. Furthermore, the insula has been shown to be involved in learning risk prediction errors, which is important for adaptive decisions (d'Acremont et al., 2009; Preuschoff et al., 2008).

In addition to the critical role of the insula in integrating interoceptive responses to guide future decisions, two other regions, namely the DMPFC and ACC, are also involved in different stages of this process. Consistent with several previous findings (Bolla et al., 2003; Critchley et al., 2001; Fukui et al., 2005; Hsu et al., 2005; Tanabe et al., 2007; Xue et al., 2009), the dorsal MPFC is involved in emotional processing associated with taking a risk. According to the somatic markers hypothesis, the dorsal MPFC is a structure that triggers somatic states from secondary inducers (e.g., uncertainty of the choice) that will be represented in the insula (Bechara and Damasio, 2005; Damasio, 1994). In contrast, we found increased ACC activation in making decisions after Norisk compared to after Riskwin. The ACC and the insula are anatomically interconnected and the co-activation of the two regions has been observed in many studies employing various emotional tasks (Craig, 2009). According to Craig (2002), the insula and ACC can be respectively regarded as limbic sensory and motor cortices that engender the feeling and motivation aspects of a given emotion. Consistently, it has been shown that damage to the insula leads to subjective feelings of impaired energy or drive, which may result from the disconnection between the insula and anterior cingulate cortex that has been associated with willed action and motor behavior (Manes et al., 1999). The DMPFC-insula-ACC circuitry thus may form an integral neural network that underlies the effect of emotional arousal on risky decision-making.

The critical role of the insula in integrating the homeostatic states, e.g., the "urge" to guide economic risky decisions, provides a neural basis for an alternative perspective on risky decision-making, which views decision making as a process of regulating homeostatic state (Paulus, 2007). Traditional approaches to understanding decision-making are based on economic theories which focus on the evaluation of various decision parameters, such as gain, loss, uncertainty, fairness and so on. Indeed, any time a behavioral economics paradigm is tested (e.g., a risk or a gamble task), these economic parameters would also change the hedonic conditions represented in the insular cortex (Craig, 2009), and the von Economo Neurons contained in the insular cortex can integrate the change in hedonic states with the visceral information (e.g., "deprivation") to signal the urge that guides decisions (Allman et al., 2005). As a result, changes in homeostatic states, as triggered by monetary gains, losses, uncertainties, excessive prices, inequity and so on, will lead to a decision that helps to balance the homeostatic state, such as taking or rejecting a gamble, purchasing or rejecting a good, and taking or rejecting an unfair offer.

Discovery of the important role of the insula in integrating homeostatic states in risky decision-making, inspired from our knowledge from electrophysiology, neuroanatomy, and clinical studies, not only provides a unifying concept about insular function that explains both clinical and neuroeconomic findings, but also furthers our understanding of many human daily-life decisions that are seemingly irrational according to economic models, such as the popularity of gambling behaviors and gambling addiction. Results we present here point to the insula (and the cognitive functions it subserves) as potential targets for therapies for gambling addiction. Future studies need to directly examine the relationship between prior risk experience, homeostatic stage changes, insular activation changes and their effects on subsequent risky behaviors by the simultaneous recording of behavioral, neural and physiological responses. Where possible, larger sample size should be used to examine sex differences (Lee et al., 2009) and other individual differences in insular function, which may be related to the personality trait of urgency and the development of addictive behaviors. D4Lesion patient and/or virtual (physical and chemical) lesion approaches should be used to examine the functional necessity of the insula in gambling addiction. Finally, biofeedback training using real-time function imaging can be used to train subjects to regulate insular activity. Progress in these lines of research will have potential clinic implications for the treatment of pathological gambling.

## Competing interest statement

The authors declare that they have no competing financial interests.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.12.097.

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