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Uncovering Putative Neural Markers of Risk Avoidance

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Making decisions that involve risk is part of everyday life. Some risks are greater than others (i.e., choosing a new job vs. choosing a new shampoo), and individuals vary in their tolerance of risk. Increased risk-taking is characteristic of specific developmental periods (i.e., adolescence) and psychopathological conditions (i.e., pathologic gambling, substance use). As a result, the neural basis of risk-taking has been the focus of numerous investigations. These studies often use “safe” decisions as a control condition rather than as a condition of interest *per se*. However, extreme avoidance of risk can also be impairing. For example, excessive avoidance of situations perceived as risky is a primary characteristic of anxiety disorders such as agoraphobia and social phobia. Therefore, identification of the neural correlates of risk avoidance can inform pathophysiological models of these disorders and their response to treatments which aim to reduce such avoidance. The present study takes an initial step in this process by using functional MRI to examine brain activity associated with risk avoidance behavior.

Converging evidence from animal and human studies implicates a distributed network of brain regions in decision-making under risk or uncertainty (Ernst & Paulus, 2005; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006; Fellows, 2004). The assessment of risk during the initial phase of decision-making involves regions implicated in reward processing, probability estimation, and action selection. For example, the orbitofrontal cortex (Elliott, Dolan, & Frith, 2000; Rogers et al., 1999) and striatum (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Delgado, Locke, Stenger, & Fiez, 2003; Rogers et al., 2004) have been shown to track reward and loss magnitude. The anterior cingulate cortex (ACC) has been implicated in conflict detection and action selection (Milham & Banich, 2005; Hampton & O’Doherty, 2007), while parietal cortex is involved in representation of possible responses (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002). Studies of risk-taking demonstrate involvement of many of these regions in the process of selecting a risky choice. For example, increased activity in ventral striatum (Kuhnen & Knutson, 2005) and ACC has been associated with an increased probability of making a risky choice (Christopoulos,

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Tobler, Bossaerts, Dolan, & Schultz, 2009). The insula has been implicated in the signaling of aversive outcomes (O'Doherty, Critchley, Deichmann, & Dolan, 2003; Simmons, Matthews, Stein, & Paulus, 2004; Clark et al., 2008) and, as such, shows increased activity during selection of risky choices over safe ones (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003). Although they have received less attention, medial posterior regions such as the posterior cingulate cortex and precuneus have also been implicated in risky decision-making. Precuneus activation has been observed in adults when making risky, as opposed to safe, decisions (Paulus et al., 2003) and studies of non-human primates show that increased neuronal activity in posterior cingulate cortex is associated with a subjective preference for risky options (McCoy & Platt, 2005).

Though fewer studies have examined the neural basis of *risk avoidance*, there is evidence that selection of safe choices involves an alternate set of prefrontal and temporal regions. For example, the inferior frontal gyrus (Christopoulos et al., 2009; Matthews, Simmons, Lane, & Paulus, 2004), dorsolateral prefrontal cortex (Fecteau et al., 2007; Gianotti et al., 2009; Knoch et al., 2006), and superior and middle temporal gyri (Matthews et al., 2004) have been implicated in the selection of safe choices. While insula activity increases during risky choices, activity in this region prior to a decision appears to predict risk avoidance (Kuhnen & Knutson, 2005). These studies suggest that selecting a safe or riskless choice is not simply the converse of making a risky choice, but likely involves unique neural processes.

The primary aim of the current study was to examine neural responses to the avoidance of risk. Towards this end, we developed a Wheel of Fortune task that allows participants to choose between taking a risk and passing on each trial, thereby avoiding risk. Based on previous studies, we predicted heightened activation in prefrontal and temporal regions associated with risk avoidance. Decision-making involves the consideration of multiple factors including the expected value of the choice, which represents the combination of the probability and magnitude of reward and loss. The current study parametrically varied these factors to examine their impact on risk avoidance and associated neural activity. We predicted that individuals would pass more often on trials involving greater risk and/or a smaller expected value. While laboratory measures provide important information regarding the neural correlates of risk avoidance, the relationship between brain activity and real-world avoidance of risk has not been thoroughly examined. A recent fMRI study found nucleus accumbens activity in response to reward to be significantly correlated with self-ratings of the predicted frequency of risky behaviors in adults and adolescents (Galvan, Hare, Voss, Glover, & Casey, 2007). However, the relationship between such self-ratings and neural activity associated with risk avoidance has not been studied. Therefore, we obtained a self-report measure of the frequency of risky behaviors to evaluate whether laboratory measures of risk avoidance and associated neural activity reflect real-world risk avoidance.

METHODS

Participants

Twenty-three right-handed native English-speaking participants with no history of psychiatric or neurological illness (confirmed by psychiatric clinical assessment) were recruited from the community (8 males; mean age: 27.6 ± 7.9 years). The study was approved by the NYU School of Medicine and New York University institutional review boards. Signed informed consent was obtained prior to participation.

Decision-Making Task

The fMRI task was a modified version of the Wheel of Fortune paradigm developed by Ernst et al. (2004) that allowed for the examination of brain responses to risky and safe decisions. During each trial, participants were shown a wheel on which the probabilities of winning and losing points were shown as red and gray sections, respectively. The point amounts that could be won or lost were printed on the wheel sections (Figure 1A). The words “Bet” and “Pass” were displayed each time, prompting participants to select one or the other option. For the present study, this “decision phase” was the period of interest. After 3 s, the wheel spun for a variable, randomly jittered period (1, 3, 5, or 7 seconds; 4 s average), and the final result was displayed for 1 s. If participants chose to bet, and the wheel landed on the red section, they would win the points indicated. Conversely, if the wheel landed on the gray section, they would lose the number of points indicated. These amounts would be added (or subtracted) to a running total that was not revealed until the end of the task. If the participants chose to pass, they still saw the outcome but no points were added or deducted from the total. Inter-trial intervals were randomly jittered, ranging between 1 and 7 s with an average of 4 seconds. Throughout the task, participants were led to believe that their performance would determine the amount of money they would receive at the end, although ultimately, all were given \$25 at the completion of the study.

Win amounts were kept constant while probability and loss amounts were manipulated orthogonally resulting in 6 different wheels that represented 4 win/loss ratios (100/0, 60/40, 40/60, 0/100) and 2 levels of expected value (+12, -12) (Figure 1B). Expected value (EV) is defined as the probability of winning multiplied by the amount that can be won [$P_W * A_W$] minus the probability of losing multiplied by the amount that can be lost [$P_L * A_L$]. Participants were not explicitly informed about the uniformity of expected values. The 0/100 wheel (100% chance of losing 12 points) and the 100/0 wheel (100% chance of winning 12 points) served as no-risk control conditions and each was presented 8 times. For the 60/40 and 40/60 wheels, the number of points that could be won was constant (120), while the number of points that could be lost varied creating two levels of EV (Figure 1B). This design also allowed for 4 levels of risk across the 40/60 and 60/40 conditions as defined by the variance of their outcomes (Figure 1B). Variance was calculated based on the possible outcomes for each wheel across all trials. Wheels with greater variance are considered to be “riskier” than those with less variability in their outcomes. Each of the 40/60 (EV+ and EV-) and 60/40 (EV+ and EV-) wheels was presented 22 times across 4 blocks.

Self-Report of Risk Avoidance

The Cognitive Appraisal of Risky Events (CARE; Fromme, Katz, & Rivet, 1997) is a questionnaire that measures attitudes towards risk and the frequency of risky behaviors. As the aim of the present study was to examine actual risk-taking behavior, only the frequency scale was used. Respondents were asked to indicate how often they participated in each of 30 risky activities in the last six months. These frequencies were summed for a total frequency score. The psychometric properties of this measure have been established (Fromme et al., 1997).

Behavioral Analyses

Analyses of behavioral data were carried out using SPSS 17.0. Repeated-measures analyses of variance were used to examine risk avoidance behavior and response times (RT) across conditions of varying probability and expected value. Paired-samples t-tests were used to examine differences in RT between betting and passing. Pearson correlation coefficients were used to evaluate the relationships between task measures and CARE ratings of risky behavior frequency.

Functional Magnetic Resonance Imaging

Data Acquisition—Scans were acquired on a research-dedicated 3.0 Tesla Siemens Allegra head-only MRI scanner with a Nova array coil. During the WOF task, functional imaging scans of 36 contiguous 3 mm axial slices were acquired using a T2*-sensitive gradient echo sequence (TR = 2000ms; TE = 30; FOV = 192; 64 × 64 matrix; in-plane resolution 3 × 3 × 3). Stimuli were projected onto a screen roughly 57 cm from the subject using an Eiki LC-XG100 projector. For registration purposes, a high resolution T1-weighted volumetric image was acquired for each participant using a magnetization prepared gradient echo sequence (MPRAGE, TR = 2500ms; TE = 4.35ms; TI = 900ms; flip angle = 8; 176 slices, FOV = 256 mm).

Preprocessing and Statistical Analyses—Data preprocessing included motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT; Jenkinson, Bannister, Brady, & Smith, 2002). Preprocessing of images also included interleaved slice timing correction, spatial smoothing using a Gaussian kernel of full-width half-maximum (FWHM) = 5mm, and high- and low-pass filtering. Registration to high resolution and/or standard images was carried out using FLIRT (Jenkinson & Smith, 2001).

First level statistical analyses were carried out for each participant using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Event-related responses during the decision phase, anchored at the presentation of the wheels, were modeled using a double gamma hemodynamic response. Predictors for each of the wheel types were included in the model (100/0, 0/100, 60/40_{EV+}, 60/40_{EV-}, 40/60_{EV+}, 40/60_{EV-}). Predictors for the feedback portion of each trial were included as events of no interest since these were not the focus of the current study.

At the individual level, initial analyses examined the effects of probability and expected value on whole brain activity during decision making using 6 contrasts. The first two compared the probabilistic, or Risk, wheels to the sure, or No-Risk, wheels, collapsing across expected value: 40/60_{EV+EV-} vs. 100/0+0/100, and 60/40_{EV+EV-} vs. 100/0+0/100 trials. The next four compared levels of probability (40/60 vs. 60/40 trials), and expected value (40/60_{EV+} vs. 40/60_{EV-}; 60/40_{EV+} vs. 60/40_{EV-}; 100/0 vs. 0/100). No significant differences were found between 40/60 and 60/40 trials or between EV+ and EV-; therefore, one analysis that contrasted the combination of all 4 probabilistic wheels with the two sure wheels, without regard to EV, was used to examine overall responses to Risk vs. No-Risk. This provided us with more power to detect differences in BOLD response between Risk and No-Risk trials. Group-level analyses were then carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003). Whole-brain random-effects analyses were conducted for each contrast of interest. Z (Gaussianised t/F) statistic images were thresholded using clusters determined by $z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, Evans, Marrett, & Neelin, 1992).

To test hypotheses about brain activity related to risk avoidance, we regressed passing behavior, as defined by the percent of 40/60 and 60/40 trials during which each participant chose to pass, on the differences in BOLD signal between the Risk and No-Risk conditions. While it would have been preferable to directly compare the trials during which participants passed to the trials during which they bet, such a strategy was not possible due to significant differences in the number of trials in each condition. For example, over half of the participants had fewer than 8 trials for three of the conditions (betting on 40/60_{EV-}, betting on 60/40_{EV-}, and passing on 60/40_{EV+}), making their data less reliable. Removal of these participants would have greatly reduced our power to conduct the needed analyses.

Finally, for post-hoc analyses and to examine the relationship between neural measures and self-reported frequency of real-world risky behaviors (based on the CARE), a binary mask was created for each of the two significant clusters from the previous analysis (passing behavior regressed on risky vs. no-risk contrast). For each individual, this mask was used to extract the mean parameter estimates from separate analyses of the Risk and No-Risk conditions, resulting in two variables representing the BOLD response to risky (40/60 + 60/40) and no-risk (100) trials for each cluster. For the purposes of illustration, time-courses of the BOLD responses to Risk and No-Risk trials were extracted to create plots showing BOLD responses across 7 TRs (14s) after cue onset.

RESULTS

Task Performance

Overall, participants provided responses (bet or pass) to at least 95% of trials, demonstrating adequate engagement in the task. Percentage of passing selections and RT were not related to sex or age.

Selection Behavior—As predicted, behavior differed significantly across trial types. During the no-risk conditions, participants passed on all trials with 100% chance of losing (0/100 wheels) and bet 98.9% of the time on the 100% chance of winning wheel (100/0 wheels). A 2 (probability level) $\times$ 2 (EV) ANOVA of passing behavior across the four risk wheel types showed significant main effects of probability ($F[1,22] = 14.80, p = .001$) and expected value ($F[1, 22] = 26.79, p < .001$) with no interaction. Participants passed more often on the 40/60 wheels (Mean = 59.1%; SD = 28.5) than the 60/40 wheels (Mean = 25.1%; SD = 23.3) and passed more often during the negative EV trials (Mean = 23.1%; SD = 7.6) than during the positive EV trials (Mean = 13.6%; SD = 7.9). See Figure 2A. In terms of risk variance, we did not find a linear effect as might have been expected. Rather, participants pass the most often during 40/60EV− trials (risk variance = 12907), and the least often during 60/40EV+ trials (risk variance = 19440). See Figure 2B.

Risk Avoidance Response Times—When comparing between selection choices (bet vs. pass), participants were significantly slower when choosing to pass (mean RT = 1224.0 msec, SD = 243.8) than when choosing to bet (mean RT = 1156.1 msec, SD = 273.1) ($t[22] = 2.86, p = .009$) across the four risk conditions. A 2 (probability) $\times$ 2 (EV) ANOVA on response times when choosing to pass showed no significant main effects of probability or expected value and no interaction.

CARE Frequency Scores—The CARE was completed by all but one participant. There were no significant correlations between CARE frequency ratings and risk avoidant (passing) behavior or response times.

Task-Related BOLD signal

Within each probabilistic condition, direct comparison of trials with positive and negative EVs (EV+ vs. EV−) failed to detect any regional activation. As a result, we collapsed across these EV levels in subsequent analyses, creating three probabilistic conditions: 40/60, 60/40, and no-risk trials (100/0 and 0/100). Direct comparison of probability levels (40/60 vs. 60/40) also revealed no significant differences; therefore, these conditions were combined to examine neural responses to risky choice. As expected based on previous studies (Ernst et al., 2005; Fellows, 2004; Krain et al., 2006), making decisions during Risk trials, compared to No-Risk trials, was associated with greater activity in dorsal ACC (BA 32/6/9), bilateral striatum, thalamus, bilateral DLPFC, right insula, occipital lobe, parietal lobe, and precuneus (Figure 3; Table 1). Conversely, decreased activity in response to Risk trials, compared to

No-Risk trials, was observed in bilateral middle temporal gyrus, posterior cingulate/precuneus, and bilateral posterior insula. Compared to females, males showed greater activity in left superior frontal gyrus when making decisions during Risk trials than during No-Risk trials. As a result, sex was used as a covariate in subsequent analyses. There was no significant effect of age.

Selection Behavior—As indicated earlier, we were unable to conduct direct comparisons of BOLD signal changes during passing and betting due to substantial disparities in the number of trials included for each condition. Therefore, to evaluate the relationship between risk avoidance and BOLD response, we included the percent-pass on Risk trials (i.e., the percent of probabilistic trials on which participants passed) in the analysis of Risk (40/60 and 60/40) vs. No-Risk (100/0 and 0/100) trials. We found a negative relationship between percent-pass and BOLD activation to Risk vs. No-Risk conditions in the precuneus and the striatum (Figure 4; Table 2). No regions showed a positive relationship between passing behavior and BOLD response. The precuneus region identified in this analysis was located between the precuneus regions positively and negatively associated with the overall Risk vs. No-Risk comparison. Further examination of these findings revealed that individuals who avoided risk more often showed less differential activation of the precuneus and striatum between Risky and No-Risk task conditions.

To examine these differences in more detail, we divided the sample into high and low risk avoiders using a median split of the percent of Risk trials passed (low: percent passing ≤ 43.7 ; high: percent passing > 43.7). Similar to the dimensional analysis discussed above, a voxelwise group comparison found greater differential striatal and precuneus responses to Risk vs. No-Risk trials in the low risk-avoiders ($n = 12$) than the high risk-avoiders ($n = 11$) ($p < .05$, uncorrected). Figure 5 illustrates the differences in activity between task conditions for each subgroup. Overall, low risk-avoiders showed significantly less activity in precuneus ($t[11] = -2.55$, $p = .03$) and striatum ($t[11] = -4.53$, $p = .001$) during No-Risk trials, relative to Risk trials. High risk-avoiders showed no significant differences in activation between these conditions (i.e., neural responses to No-Risk trials were equal to responses to Risk trials). This lack of differentiation between conditions for the high risk-avoiders is accounted for by differences in responses to the No-Risk trials. Between-group analyses showed moderate to large subgroup differences in responses to the No-Risk wheels in striatum ($t[21] = -2.06$, $p = .05$) and precuneus ($t[21] = -1.36$, $p = .18$) with no differences in response to the Risk wheels. In both cases, high risk-avoiders showed greater activation (or absence of deactivation), relative to the low risk-avoiders. No differences were found between No-Risk conditions (+100 vs. -100). No other regions showed activation that was related positively or negatively with this performance measure.

Finally, response times were not significantly associated with any regional activation.

CARE Frequency Ratings—We examined the relationship between CARE ratings and neural activity in the regions of striatum and precuneus associated with risk avoidance. There was no relationship between CARE ratings and striatal or precuneus activity based on the Risk vs. No-Risk contrast. However, similar to the previous analysis, which suggested that high risk-avoiders exhibited stronger activation of the precuneus and striatum during No-Risk trials than low risk-avoiders, the self-reported frequency of risky behaviors was negatively correlated with precuneus activity during No-Risk trials ($r[22] = -.50$; $p = .02$; Figure 6). There was a moderate negative correlation between the same frequency measure and striatal activity during No-Risk trials but this was not statistically significant ($r[22] = -.26$, $p = .25$). Additional voxelwise analyses examining the regression of CARE scores against the Risk vs. No-Risk contrast across the whole brain did not find any significant results.

DISCUSSION

The aim of this study was to examine the neural substrates of risk avoidance during a risky decision-making game. We found that individuals with a greater tendency to avoid risk by choosing to pass rather than bet, showed no differential neural activation in precuneus and striatum between sure and probabilistic conditions. By contrast, neural activity in precuneus and striatum in low risk-avoiders was significantly greater during Risk conditions relative to No-Risk trials. This laboratory observation was confirmed by self-report of “real-world” risk taking, which showed a similar relationship with precuneus activity during No-Risk trials. If this relationship is independently replicated, it may represent a neural marker of risk avoidance that could be applied to clinical settings.

We observed activity in ACC, striatum, insula, dorsolateral prefrontal cortex, thalamus, precuneus, and parietal lobe when participants were faced with making a risky decision. This is consistent with previous work (Ernst et al., 2005; Fellows, 2004; Krain et al., 2006), suggesting that our Wheel of Fortune task was tapping circuits similar to those observed in other decision-making studies. We were unable to differentiate BOLD responses to different levels of probability and expected value as have been observed elsewhere (Tobler, O’Doherty, Dolan, & Schultz, 2007; Smith et al., 2009). Possible explanations include limited power from too few trials in each condition and our inability to orthogonalize loss magnitude and expected value because of limits on task duration. The lack of differential BOLD responses to EV+ and EV− conditions may also have resulted from small size of the EVs and/or the short distance between them (i.e., 24). Modification of this task will be needed to examine these factors more closely in future studies.

One of the unique findings of this study is the relationship of BOLD activity during the No-Risk conditions (100/0 and 0/100 wheels) with behavioral risk avoidance, i.e., high propensity for passing in response to a risky decision, providing a putative neural marker of risk avoidance. The neural responses of individuals who took fewer risks (passed more often) during the task did not differentiate between certainty and risk. Conversely, individuals who chose to take more risks (passed less often), showed relatively greater striatal and precuneus activity in response to Risk trials than to No-Risk trials.

The striatum has frequently been implicated in risky decision-making, particularly due to its role in evaluating reward. Recent evidence suggests that caudate responses to decision-making and reward are contingent on participant motivation (Delgado, Stenger, & Fiez, 2004), which may explain the current findings. Both high and low risk-avoiders demonstrated increased striatal activity in response to risky decisions, where motivational value is high. However, during trials where the chance of winning or losing was 100%, low risk-avoiders showed striatal deactivation, perhaps because of the absence of potential reward prediction error, i.e., motivation. Conversely, individuals who tended to avoid risk may have been equally motivated during the No-Risk trials as during the Risk trials, accounting for similar levels of caudate activity.

The precuneus has only recently become a focus in human neuroimaging studies. It has been implicated in a wide range of cognitive functions including visuospatial imagery, episodic memory, and self-referential processes (Cavanna & Trimble, 2006; Johnson et al., 2006). The present findings highlight the functional complexity of the precuneus and its putative role in risky decision-making. For example, group analyses found a dorsal region of precuneus to be more active during Risk decisions than No-Risk decisions, which is consistent with previous findings (Paulus et al., 2003). We also found a more anterior region bordering posterior cingulate cortex to show greater activity during No-Risk decisions. The region of precuneus associated with risk avoidant behavior was located between these two

areas with only minor overlap. This region related to risk avoidance fell primarily in sensorimotor areas with some extension into central precuneus areas involved in higher cognitive functions such as self-processing and mentalizing (Margulies et al., 2009; Cavanna et al., 2006). Similar to the striatal findings, this suggests that high risk-avoiders may be more involved in the task during No-Risk conditions than those who take more risks. The role of this region in risk avoidance is further supported by the significant relationship between precuneus activity during the task and self-reported frequency of real-world risky behaviors. Recent studies of anxiety disorders, which are often characterized by significant risk avoidance, implicate similar regions of the precuneus (Gentili et al., 2009; McClure et al., 2007; Warwick, Carey, Jordaan, Dupont, & Stein, 2008). These results highlight the importance of distinguishing between dorsal and ventral areas of the precuneus, particularly given recent work (Margulies et al., 2009) that illustrates differential patterns of functional connectivity between these areas. Future work should aim to functionally dissect the precuneus with regard to risk taking and avoidance of risk.

There were several limitations of the current study. First, we were unable to conduct direct comparisons of BOLD activity between passing and betting trials because of the significant confound between behavior and wheel type. Direct comparison of betting vs. passing would have entailed excessively uneven proportions of 40/60_{EV+}, 40/60_{EV-}, 60/40_{EV+}, 60/40_{EV-} trials. To mitigate this limitation, one strategy in future work would be to include greater variation in levels of probability and expected value as a way to better equate the frequency of betting and passing. Second, participant payments were not contingent on the specific outcomes of each trial. We speculate that including real contingencies in our design might have increased participant investment in the task and altered decisions to bet or pass. Third, the timing used in the current task design did not allow for examining separately distinct cognitive processes involved in decision-making such as choice evaluation and selection. Future investigations are needed to examine whether the current findings are attributed to activity in response to evaluating the choice stimuli or to the process of making a selection. Finally, we did not find any association between risk avoidance and activity in prefrontal or temporal regions, as has been previously reported (Christopoulos et al., 2009; Matthews et al., 2004; Fecteau et al., 2007). This may be due to methodological differences and the use of an overall regressor to represent risk avoidance rather than direct trial-by-trial comparisons of risk-taking and risk avoidance. Additionally, the design of the task limited our ability to test alternative models such as neuroeconomic models of risk aversion. Future studies are needed to replicate and extend the current findings using a task that takes these limitations into account and provides the opportunity to test alternative models of risk avoidance across a wider range of risk levels.

Despite these limitations, our preliminary findings suggest that brain activity in response to No-Risk or safe trials correlates with risk avoidance during risky conditions. Further, BOLD responses to certainty, particularly in the precuneus, appear to reflect risk avoidance more broadly, as evidenced by the relationship with self-reported frequency of risky behavior. These findings also support the conclusion that the neural network involved in avoidance of risk differs from that associated with risk taking. This provides a compelling rationale for further examination of the BOLD correlates of risk avoidance, particularly in individuals with anxiety disorders, who suffer impairment due to their avoidance of risky situations.

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Reference List

- Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in fMRI. *Neuroimage*. 2003; 20:1052–1063. [PubMed: 14568475]
- Bunge SA, Hazeltine E, Scanlon MD, Rosen AC, Gabrieli JD. Dissociable contributions of prefrontal and parietal cortices to response selection. *Neuroimage*. 2002; 17:1562–1571. [PubMed: 12414294]
- Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006; 129:564–583. [PubMed: 16399806]
- Christopoulos GI, Tobler PN, Bossaerts P, Dolan RJ, Schultz W. Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *J Neurosci*. 2009; 29:12574–12583. [PubMed: 19812332]
- Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain*. 2008; 131:1311–1322. [PubMed: 18390562]
- Delgado MR, Locke HM, Stenger VA, Fiez JA. Dorsal striatum responses to reward and punishment: Effects of valence and magnitude manipulations. *Cognitive, Affective, and Behavioral Neuroscience*. 2003; 3:27–38.
- Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA. Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*. 2000; 84:3072–3077. [PubMed: 11110834]
- Delgado MR, Stenger VA, Fiez JA. Motivation-dependent responses in the human caudate nucleus. *Cereb.Cortex*. 2004; 14:1022–1030. [PubMed: 15115748]
- Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb.Cortex*. 2000; 10:308–317. [PubMed: 10731225]
- Ernst M, Nelson EE, McClure EB, Monk CS, Munson S, Eshel N, et al. Choice selection and reward anticipation: An fMRI study. *Neuropsychologia*. 2004; 42:1585–1597. [PubMed: 15327927]
- Ernst M, Paulus MP. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*. 2005; 58:597–604. [PubMed: 16095567]
- Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci*. 2007; 27:12500–12505. [PubMed: 18003828]
- Fellows LK. The cognitive neuroscience of human decision making: a review and conceptual framework. *Behav.Cogn Neurosci.Rev*. 2004; 3:159–172. [PubMed: 15653813]
- Fromme K, Katz EC, Rivet K. Outcome expectancies and risk-taking behavior. *Cognitive Therapy and Research*. 1997; 21:421–442.
- Galvan A, Hare T, Voss H, Glover G, Casey BJ. Risk-taking and the adolescent brain: who is at risk? *Dev.Sci*. 2007; 10:F8–F14. [PubMed: 17286837]
- Gentili C, Ricciardi E, Gobbini MI, Santarelli MF, Haxby JV, Pietrini P, et al. Beyond amygdala: Default Mode Network activity differs between patients with social phobia and healthy controls. *Brain Res.Bull*. 2009; 79:409–413. [PubMed: 19559343]
- Gianotti LR, Knoch D, Faber PL, Lehmann D, Pascual-Marqui RD, Diezi C, et al. Tonic activity level in the right prefrontal cortex predicts individuals' risk taking. *Psychol.Sci*. 2009; 20:33–38. [PubMed: 19152538]
- Hampton AN, O'Doherty JP. Decoding the neural substrates of reward-related decision making with functional MRI. *Proc.Natl.Acad.Sci.U.S.A*. 2007; 104:1377–1382. [PubMed: 17227855]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17:825–841. [PubMed: 12377157]
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*. 2001; 5:143–156. [PubMed: 11516708]
- Johnson MK, Raye CL, Mitchell KJ, Touryan SR, Greene EJ, Nolen-Hoeksema S. Dissociating medial frontal and posterior cingulate activity during self-reflection. *Soc.Cogn Affect.Neurosci*. 2006; 1:56–64. [PubMed: 18574518]

- Knoch D, Gianotti LR, Pascual-Leone A, Treyer V, Regard M, Hohmann M, et al. Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. *J Neurosci*. 2006; 26:6469–6472. [PubMed: 16775134]
- Krain AL, Wilson AM, Arbuckle R, Castellanos FX, Milham MP. Distinct neural mechanisms of risk and ambiguity: A meta-analysis of decision-making. *Neuroimage*. 2006; 32:477–484. [PubMed: 16632383]
- Kuhnen CM, Knutson B. The neural basis of financial risk taking. *Neuron*. 2005; 47:763–770. [PubMed: 16129404]
- Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, et al. Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc.Natl.Acad.Sci.U.S.A.* 2009; 106:20069–20074. [PubMed: 19903877]
- Matthews SC, Simmons AN, Lane SD, Paulus MP. Selective activation of the nucleus accumbens during risk-taking decision making. *Neuroreport*. 2004; 15:2123–2127. [PubMed: 15486494]
- McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJR, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Arch.Gen.Psychiatry*. 2007; 64:97–106. [PubMed: 17199059]
- McCoy AN, Platt ML. Risk-sensitive neurons in macaque posterior cingulate cortex. *Nat.Neurosci*. 2005; 8:1220–1227. [PubMed: 16116449]
- Milham MP, Banich MT. Anterior cingulate cortex: an fMRI analysis of conflict specificity and functional differentiation. *Hum.Brain Mapp*. 2005; 25:328–335. [PubMed: 15834861]
- O'Doherty J, Critchley H, Deichmann R, Dolan RJ. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *Journal of Neuroscience*. 2003; 23:7931–7939. [PubMed: 12944524]
- Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*. 2003; 19:1439–1448. [PubMed: 12948701]
- Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, et al. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J.Neurosci*. 1999; 19:9029–9038. [PubMed: 10516320]
- Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, et al. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biol.Psychiatry*. 2004; 55:594–602. [PubMed: 15013828]
- Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport*. 2004; 15:2261–2265. [PubMed: 15371746]
- Smith BW, Mitchell DG, Hardin MG, Jazbec S, Fridberg D, Blair RJ, et al. Neural substrates of reward magnitude, probability, and risk during a wheel of fortune decision-making task. *Neuroimage*. 2009; 44:600–609. [PubMed: 18804540]
- Tobler PN, O'Doherty JP, Dolan RJ, Schultz W. Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. *J Neurophysiol*. 2007; 97:1621–1632. [PubMed: 17122317]
- Warwick JM, Carey P, Jordaan GP, Dupont P, Stein DJ. Resting brain perfusion in social anxiety disorder: a voxel-wise whole brain comparison with healthy control subjects. *Prog.Neuropsychopharmacol.Biol.Psychiatry*. 2008; 32:1251–1256. [PubMed: 18485554]
- Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*. 2001; 14:1370–1386. [PubMed: 11707093]
- Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*. 1992; 12:900–918. [PubMed: 1400644]

Figure 1. Wheel of Fortune task design. (A) Task stimuli presented during each trial. (B) Expected values (EV), risk variance, probability, and magnitude of loss and gain for each wheel.

Figure 2. (A) Percent of trials passed across trials varying in probability and expected value (EV). (B) Percent of trials passed across the four Risk trial types trials in ascending order of risk variance.

Figure 3. Clusters of significant activation for the Risk > No-Risk contrast (orange) and No-Risk > Risk contrast (blue). Clusters survive Gaussian Random Field (GRF) correction at $p < .05$.

Figure 4.

Brain activity associated with passing during Risk trials. (A) Precuneus ($x = -2$) and striatal ($z = -4$) clusters (GRF corrected, $p < .05$) showing a significant relationship between passing behavior during Risk trials and activity based on the Risk vs. No-Risk contrast. (B) Scatterplot demonstrating the relationships between percent passing during Risk trials and brain activity based on the Risk vs. No-Risk contrast. Solid line indicates relationship with precuneus and dotted line indicates relationship with striatum.

Figure 5. Precuneus and striatal responses to Risk and No-Risk trials for high and low risk avoiders. Bar graphs represent the average across all time points. Line graphs represent the separate timecourses for Risk and No-Risk trials. Blue bars and lines represent BOLD responses to No-Risk trials; Green bars and lines represent BOLD responses to Risk trials. * $p < .05$; ** $p < .005$.

Figure 6. Scatterplot illustrating the significant relationship between CARE ratings of the frequency of risky behavior and precuneus activity during No-Risk trials.

Table 1

Regional brain activity associated with risky vs. no-risk trials.

Region	Cluster Size	x	y	z	Z
Prob40+60 > Prob100					
Precuneus	6872	24	-60	52	6.22
		24	-66	58	5.56
		24	-66	48	5.31
Superior parietal lobule		24	-60	60	5.8
Fusiform gyrus		22	-92	-10	5.14
Middle occipital gyrus		38	-88	4	5.12
Lateral occipital cortex	5909	-26	-90	2	6.04
Middle occipital gyrus		-24	-96	10	5.09
Cuneus		-20	-96	4	5.51
		-24	-84	14	5.2
Precuneus		-26	-78	24	5.15
Lingual gyrus		-16	-98	0	5.24
Caudate	3003	-8	6	-4	4.96
		14	14	0	4.59
		10	8	2	4.5
		12	6	-4	4.42
		8	8	-2	4.42
Brainstem		8	-28	-12	4.12
Cingulate gyrus	1732	4	22	44	5.24
		-4	30	30	4.46
		4	38	24	3.37
Medial frontal gyrus		4	30	38	5.1
		-6	12	50	3.87
Precentral gyrus	987	-24	-6	52	4.65
		-36	-4	60	3.61
		-38	-6	50	3.55
		-38	-10	52	3.51

Region	Cluster Size	x	y	z	Z
Middle frontal gyrus		-32	0	64	4.12
		-28	0	60	4.07
Middle frontal gyrus	910	30	0	56	4.38
Medial frontal gyrus		22	-4	52	4.29
Cingulate gyrus		24	4	42	3.33
		24	8	46	3.27
Middle frontal gyrus	542	48	32	30	4.14
		44	34	22	3.96
		40	32	28	3.88
		40	26	46	3.22
		36	22	54	3.08
Superior frontal gyrus		36	24	50	3.03
Insula	506	30	24	0	4.1
		32	22	6	3.46
		32	24	-4	3.98
		36	18	-4	3.96
Inferior frontal gyrus		46	20	8	3.25
Frontal pole	435	36	60	12	3.94
		36	54	4	3.65
		40	58	-10	3.5
		46	52	10	3.16
Middle frontal gyrus	353	-52	20	34	4.01
		-50	24	22	3.62
Precentral gyrus		-52	0	36	3.02
Prob100 > Prob40+60					
Middle temporal gyrus	4372	64	-44	4	4.99
		62	-50	2	4.84
		60	-56	6	4.8
		66	-48	6	4.75
Angular gyrus		54	-54	18	4.66
Inferior parietal lobe		64	-34	28	4.96

Region	Cluster Size	x	y	z	Z
Inferior parietal lobe	3479	-64	-30	24	5.2
		-64	-38	32	4.93
		-62	-42	34	5.19
Middle temporal gyrus		-62	-56	2	4.52
		-64	-52	8	4.51
		-62	-54	-8	4.45
Cuneus	3258	6	-88	22	5
		6	-90	18	4.89
Precuneus		-4	-48	40	4.41
		-4	-50	34	4.26
		-4	-60	10	4.6
Cingulate gyrus		-14	-38	38	4.05
Precentral gyrus	545	-58	8	6	4.16
		-56	8	10	4.02
		-52	2	8	3.06
Insula		-36	-6	6	3.57
		-38	4	2	3.53
		-34	6	4	3.42

Table 2

Significant areas of activity associated with passing behavior

Region	Cluster Size	x	y	z	Z
Caudate	402	6	10	0	3.58
		12	14	-6	3.19
		0	4	-2	2.84
Thalamus		2	-2	4	3.13
		-10	-2	10	3.08
Lentiform nucleus		14	4	-6	2.88
Precuneus	401	0	-54	58	3.81
		-4	-58	48	3.8
		2	-58	56	3.58
		0	-60	38	3.18
		20	-68	58	3.05
Superior parietal lobule		10	-64	66	3.23