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Medial frontal cortex and anterior insula are less sensitive to outcome predictability when monetary stakes are higher

Emily R. Stern,[1] Richard Gonzalez,[2] Robert C. Welsh,[3] and Stephan F. Taylor[3]

[1]Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA, [2]Department of Psychology, University of Michigan, Ann Arbor, MI 48109, USA, and [3]Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA

Prior research links greater activation of posterior medial frontal cortex (pMFC) and anterior insula (AI) with decreasing outcome predictability during decision making, as measured by decreasing probability for the more likely outcome out of two or increasing outcome variance. In addition to predictability, much work indicates that the magnitude or 'stakes' of the outcome is also important. Despite the interest in the neural correlates of these decision variables, it is unknown whether pMFC and AI are differentially sensitive to predictability when magnitude is varied. This study examined brain activity during decision making in relation to decreasing outcome predictability for low as compared with high magnitude decisions. For low magnitude decisions, reduced predictability of the outcome was associated with greater activity in pMFC and bilateral AI, replicating prior studies. In contrast, there was no relationship between predictability and brain activity for high magnitude decisions, which tended to elicit greater pMFC and AI activity than low magnitude decisions for more predictable outcomes. These data indicate that the relationship between outcome predictability and pMFC and AI activity during decision making depends on magnitude, and suggest that these regions may be responding to the motivational salience of the decision rather than predictability information *per se*.

Keywords: decision making; salience; uncertainty; probability; risk; magnitude

INTRODUCTION

Many studies have linked regions of posterior dorsal medial frontal cortex (pMFC) and anterior insula (AI) to choice behavior (for a review, see Platt and Huettel, 2008). In the judgment and decision-making literature, 'risk' typically refers to a class of decision problems where the probabilities associated with the outcomes are known and uncertain (probability for an outcome is <1.0). Risk has been measured as the variance between possible outcomes (Preuschoff *et al.*, 2006; Preuschoff *et al.*, 2008; Christopoulos *et al.*, 2009), which increases non-linearly as probabilities become closer to a uniform distribution over possible outcomes. Similarly, 'uncertainty' has been operationalized as variance (Tobler *et al.*, 2007), or in terms of linear decreases in the probability of the more likely outcome out of two (Critchley *et al.*, 2001; Volz *et al.*, 2003; Huettel *et al.*, 2005; Krain *et al.*, 2006; Stern *et al.*, 2010). Although risk and uncertainty have occasionally been used somewhat interchangeably (Critchley *et al.*, 2001; Platt and Huettel, 2008; Preuschoff *et al.*, 2008), in other approaches uncertainty refers to the specific case where outcome probabilities are not known (e.g. uncertainty due to ambiguity, Camerer and Weber, 1992). To avoid confusion, in this study we describe decision options in terms of outcome *predictability* (Paulus *et al.*, 2002). Within this framework, predictability decreases as the probability for the more likely outcome decreases and outcome variance increases. For example, it is more difficult to predict whether an umbrella will be needed if there is a 70% chance of sun and 30% chance of rain than if there is a 95% chance of sun and a 5% chance of rain, as the probability of the more likely outcome of sun is decreased in the former case—and variance between outcomes is larger—than in the latter case. Several studies have found that, as outcome predictability decreases, activity in pMFC and AI increases (Critchley *et al.*, 2001; Paulus *et al.*, 2002; Volz *et al.*, 2003; Huettel *et al.*, 2005; Krain *et al.*, 2006; Preuschoff *et al.*, 2008; Mohr *et al.*, 2010; Stern *et al.*, 2010).

Decision making is a complex behavior that is influenced by multiple factors. Not only do outcome probabilities influence choice behavior and brain activity, but the magnitude or the 'stakes' of the outcome is also critical (Knutson *et al.*, 2005; Tobler *et al.*, 2007; Yacubian *et al.*, 2007; Christopoulos *et al.*, 2009; Smith *et al.*, 2009). Thus, although there may be both a 30% chance of rain for your morning commute and a 30% chance of death from your upcoming surgery, the magnitude or 'stakes' is greater for the decision for surgery, despite equivalent probabilities. While prior studies have compared neural regions processing probability and magnitude (Knutson *et al.*, 2005; Tobler *et al.*, 2007; Yacubian *et al.*, 2007; Smith *et al.*, 2009), to our knowledge no studies have examined whether pMFC and AI are differentially sensitive to decreasing predictability during decision making when the stakes of outcomes are varied. An investigation of how the brain processes outcome predictability for low *vs* high stakes decisions is relevant for understanding decision-making abnormalities in psychiatric disorders characterized by altered perceptions of likelihood for high stakes negative outcomes, such as obsessive–compulsive disorder (Steketee *et al.*, 1998; Sookman and Pinard, 2002). To determine how pMFC and AI respond to decreasing predictability when the stakes are varied, the current functional magnetic resonance imaging (fMRI) study examined activity in these regions in relation to decreasing predictability (as measured by decreasing probability for the more likely outcome and by increasing outcome variance) separately for low magnitude (winning or losing 5 cents) and high magnitude (winning or losing 20 cents) decisions.

Outside the domain of decision making, pMFC and AI co-activate in a variety of tasks including emotion/interoception (Critchley *et al.*, 2004; Kober *et al.*, 2008), conflict monitoring and error processing (van Veen *et al.*, 2001; Taylor *et al.*, 2007; Pochon *et al.*, 2008) and attention shifting (Wager *et al.*, 2004). It has been suggested that these regions are responsible for the more general detection of salient

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Correspondence should be addressed to Emily R. Stern, Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave Levy Place, Box 1230, New York, NY 10029, USA. E-mail: emily.stern@mssm.edu

information (Seeley *et al.*, 2007; Sridharan *et al.*, 2008), which may explain their frequent activation. Thus, it is possible that pMFC and AI activity does not reflect outcome predictability *per se* but instead signals the general salience of the decision (which is expected to be sensitive to several factors, one of which is outcome predictability). Our comparison of pMFC and AI activity to decreasing predictability across magnitudes will help inform this question. Specifically, if pMFC and AI track outcome predictability, there should be no difference in the pattern of predictability-related activations for low and high magnitude decisions. However, if pMFC and AI activity are sensitive to the general salience of the decision, high magnitude decisions should elicit a differential pattern of neural responses to predictability than low magnitude decisions.

MATERIALS AND METHODS

Subjects and task

Seventeen subjects (mean age: 21.6 years, range: 18–32 years; eight males, nine females) without history of psychiatric disorder or major medical illness participated in the study. The research was approved by the University of Michigan Medical School Institutional Review Board, and written informed consent was obtained from all subjects according to the Declaration of Helsinki. The 'incentive card task' (ICT) (Figure 1) is based on prior studies examining how the brain processes predictabilty (Critchley *et al.*, 2001; Krain *et al.*, 2006; Preuschoff *et al.*, 2006; Preuschoff *et al.*, 2008). In this task, subjects are presented with two cards that are selected from one deck containing nine cards numbered one through nine. One of the cards is displayed face-up ('shown' card), whereas the other is displayed face-down ('hidden' card), and the task of the subjects is to decide whether the number on the hidden card is higher or lower than the number on the shown card. As the deck from which the cards are drawn only contains nine cards, the % chance of the hidden card being higher or lower varies between 100% ('1' or '9' card), 87.5% ('2' or '8' card), 75% ('3' or '7' card), 62.5% ('4' or '6' card) and 50% ('5' card). In addition to this probability manipulation, which has been examined in several studies (Critchley *et al.*, 2001; Paulus *et al.*, 2002; Volz *et al.*, 2003; Huettel *et al.*, 2005; Krain *et al.*, 2006), half of trials carry 'high magnitude' outcomes, resulting in a loss/gain of 20 cents if the decision is incorrect/correct, and the other half of trials carry 'low magnitude' outcomes resulting in a loss/gain of only 5 cents. The inclusion of this magnitude factor allowed us to determine whether the neural mechanisms of decreasing predictability differ based on the relative magnitude of the decision. All monetary gains and losses were tallied throughout the task and determined a real bonus at the end of the experiment.

The ICT is composed of 160 trials in total, with 16 trials occurring in each of the 10 probability/magnitude combinations (5 probabilities for each of two magnitudes) over 5 runs (32 trials per run). At the beginning of each trial, the magnitude of the outcome is shown for 1000 ms, followed by the presentation of the two cards ('decision period') for 1750 ms, during which time a response of 'higher' or 'lower' is made. Responses not made within this time frame were infrequent and were considered omission errors (mean omission count: 1.8). Feedback regarding the amount won or lost is then presented for 1400 ms. To reduce multicollinearity between decision and feedback events, jittered

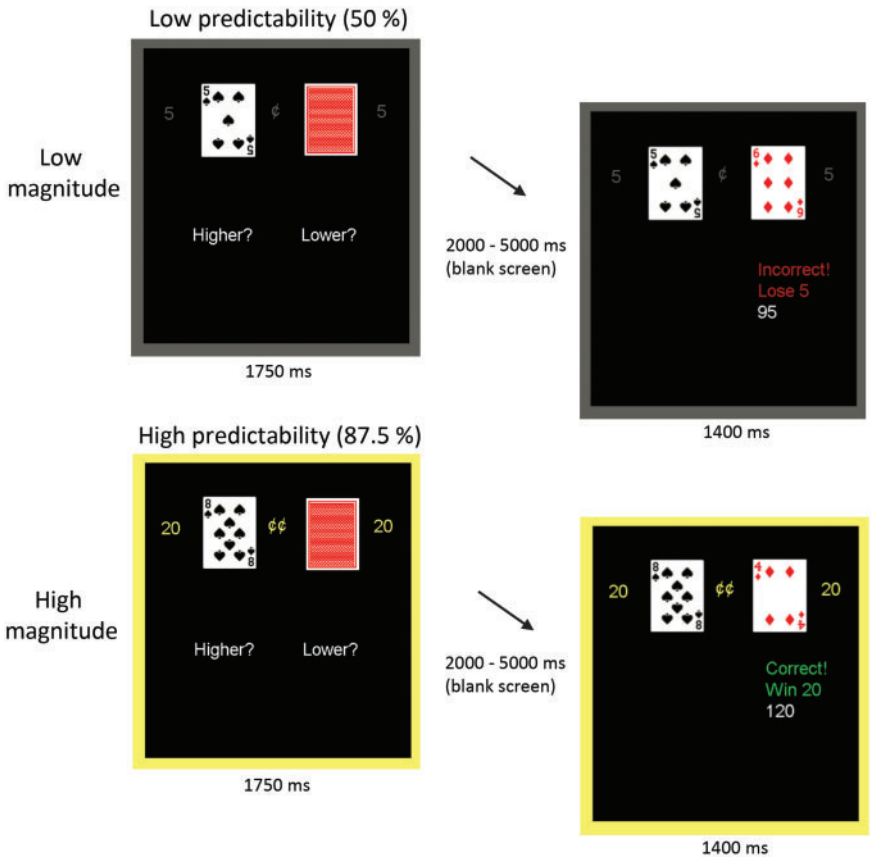

Fig. 1 Subjects decide whether the hidden card is higher or lower than the shown card. Predictability is parametrically varied between 50% and 100% based on the number of the shown card and reflects the % chance for the more likely outcome. Half of decisions have high magnitude outcomes (involving a gain or loss of 20 cents), whereas half have low magnitude outcomes (involving a gain or loss of 5 cents). In the example shown, the subject chooses 'lower' for both trials.

blank screens were presented for an average of 3500 ms (range: 2000–5000 ms) in-between the decision and feedback screens as well as the feedback screen and the beginning of the next trial.

Functional MRI acquisition and preprocessing

MRI scanning occurred on a GE 3-T Signa scanner. A T1-weighted image was acquired in the same prescription as functional images to facilitate coregistration. Functional images were acquired with a T2*-weighted, reverse spiral acquisition sequence (Gradient echo, Repetition time = 2000, Echo time = 30, Flip angle = 90, Field of view = 20 cm, 40 slices, 3 mm thickness, skip = 0, matrix diameter equivalent to 64 × 64) sensitive to signal in ventral medial frontal regions (Yang *et al.*, 2002). Subjects underwent five runs, each consisting of 185 volumes plus 4 initial, discarded volumes to allow for thermal equilibration of scanner signal. After acquisition of functional volumes, a high resolution T1 SPGR scan was obtained for anatomic normalization.

Images were presented by a BrainLogics (PST Inc., Pittsburgh, PA, USA) digital MR projector, which provides high-resolution video (1024 × 768) by back projection. Physiologic signals (heart rate and respiration) were removed from the data using RETROICOR (Glover *et al.*, 2000) for all but one subject. Data were then realigned using MCFLIRT (Jenkinson *et al.*, 2002) and slice-time corrected using slicetimer (interpolated with an eight-point sinc kernel multiplied by a Hanning window) (FSL, Analysis Group, FMRIB, Oxford, UK). The remainder of preprocessing was performed using the Statistical Parametric Mapping (SPM) 5 package (Wellcome Institute of Cognitive Neurology, London, UK), and included coregistration, normalization to the MNI152 brain (an average of 152 T1 images from the Montreal Neurological Institute) and spatial smoothing with a 5 mm isotropic Gaussian kernel. Two subjects had fewer than five runs of data used for analysis. Data from one run for one subject were lost due to technical error, and data from two runs from another subject were excluded because of excessive omission errors. Behavioral analyses were performed only with the data included in fMRI analysis.

Data analysis

Behavioral

Behavioral analyses examined mean reaction times (RTs) and accuracy (percent incorrect decisions) for the 10 conditions (5 probabilities × 2 magnitudes) as dependent measures in two separate multiple regression models. The accuracy measure was examined in order to check whether participants were generally choosing according to probability. Given that the 'correct' answer was determined from the real outcome, which was random, incorrect decisions were expected even when subjects performed optimally. In particular, ∼50% incorrect decisions were expected on 50% probability trials, with the error rate decreasing as the probability for the more likely outcome increased.

Several predictors were used to model effects of probability and magnitude on RT and accuracy. The linear effect of probability for the more likely outcome was used as a continuous variable (100%, 87.5%, 75%, 62.5% and 50%, mean-centered) and magnitude (low *vs* high, mean-centered) was used as a categorical variable. The interaction between probability and magnitude was also specified. A quadratic term for the probability variable was included to examine non-linear effects, as was the interaction between the quadratic term and magnitude. Finally, 16 subject factors were included to account for the repeated measures.

Functional MRI analysis

Primary analyses. All analyses of fMRI blood-oxygen dependent level (BOLD) signal were event-related. Two models were created for primary analyses. Model 1 specified two regressors for the decision period (onset at the time the cards are presented on-screen, event durations set to RT to make the decision), one for each magnitude (low and high). Each of these regressors was parametrically modulated by the % chance for the more likely outcome (cards 1 and 9: 100%; cards 2 and 8: 87.5%; cards 3 and 7: 75%; cards 4 and 6: 62.5%; card 5: 50%), so that linear decreases in probability (i.e. decreases in predictability) for low magnitude decisions could be examined separately from linear decreases in probability for high magnitude decisions. Regressors for the presentation of the outcome were included in the model to account for variance but are not the focus of the current analysis. Each regressor was convolved with the canonical hemodynamic response function using the general linear model. The average correlation between any two regressors in the same run in the model was 0.05 (average minimum correlation: 0.006, average maximum correlation: 0.14), indicating very low collinearity between events. Omission trials where subjects did not make a decision on time were infrequent (mean number of omission trials: 1.8, standard deviation: ±2.9 trials) and were not modeled.

First-level contrasts examined negative correlations between brain activity and probability for the more likely outcome (i.e. regions showing increasing activity for reduced outcome predictability) for low magnitude (corr-LO) and high magnitude (corr-HI) decisions separately, as well as their comparison (corr-LO > corr HI). For completeness, contrasts were also performed for the main effect of decreasing probability (averaged across high and low magnitudes) and the main effect of magnitude (high > low magnitude decisions, averaged across probability). One-sample *t*-tests examined whole-brain group effects for these contrasts, with a threshold of $P < 0.05$, cluster-level corrected for multiple comparisons using topological false discovery rate as implemented in SPM8. As activations of pMFC and bilateral AI were of a priori interest, effects were also interrogated within a region of interest (ROI) (voxelwise $P < 0.005$ with a cluster extent of 20 voxels) constructed by combining three 20 mm radius spheres located around coordinates in pMFC (4, 30, 30), left AI (−32, 24, −6) and right AI (37, 25, −4), identified by Sridharan *et al.* (2008).

To further examine effects found in model 1, parameter estimates from regions showing significant effects were plotted for each of the 10 different conditions (5 probabilities × 2 magnitudes). To obtain these parameter estimates, a second model (model 2) was run that specified separate regressors for the decision periods of all 10 conditions. As with model 1, outcome regressors of no interest were also specified.

Secondary analyses.

- RT-restricted model: As described in the 'Results' section, there was a significant relationship between probability and RT, with decisions on trials with lower probability for the more likely outcome (i.e. trials with reduced predictability) associated with slower response times, consistent with prior studies (Grinband *et al.*, 2006; Krain *et al.*, 2006; Stern *et al.*, 2010; Daniel *et al.*, 2011). Despite the fact that RT slowing is expected to occur as a behavioral correlate of decreasing predictability, it is also possible that RT slowing could be influenced by non-specific factors such as arousal, effort or attention that may not be related to predictability *per se* (Heekeren *et al.*, 2008). If this were the case, our primary analysis could be detecting brain activity related to these non-specific factors in addition to probability. To explore this issue, we performed an analysis on a restricted set of trials where the relationship between RT slowing and probability was eliminated. In this analysis, the 62.5% slowest decisions where there was higher probability for the more likely outcome (i.e. higher predictability, 100%, 87.5% and 75% trials) and the 62.5% fastest decisions where there was lower probability (i.e. lower predictability, 62.5% and 50% trials) were selected separately for low and high

magnitude decisions, which effectively decoupled RT from probability (see behavioral results). As in model 1 of the primary analysis, brain activity during the decision period was parametrically modulated by probability separately for low and high magnitude decisions, and contrasts (corr-LO, corr-HI and corr LO > corr HI) examined activity related to decreasing probability for the more likely outcome (i.e. decreasing predictability) within the whole brain as well as in the ROI consisting of pMFC and bilateral AI. Decision trials that were not included in this restricted RT range as well as outcome phases were specified in the model to capture variance but not analyzed further.

- Variance model: The primary analysis using probability as a modulator of activity was modeled after several prior studies examining the neural correlates of decreasing outcome predictability (which these studies refer to as uncertainty) by looking at the linear effect of probability (Critchley *et al.*, 2001; Volz *et al.*, 2003; Huettel *et al.*, 2005; Krain *et al.*, 2006). However, other approaches have used a quadratic measure of variance (Preuschoff *et al.*, 2006; Tobler *et al.*, 2007; Preuschoff *et al.*, 2008), which is calculated as the mean squared deviation from the expected outcome (Markowitz, 1952; Preuschoff *et al.*, 2006) and increases as predictability decreases. To examine the relationship between brain activity and increasing variance, we ran an additional model where low and high magnitude decisions were parametrically modulated by variance, using a formula adapted from Tobler *et al.* (2007):

$$\text{variance} = [P \times (m - \text{EV})^2] + [(1 - P) \times (-m - \text{EV})^2],$$

where P is the probability for more likely outcome, m is the magnitude (5 or 20) and EV is the expected value ($P \times m$). Positive correlations with variance were examined for each magnitude separately (corr-LO and corr-HI), as well as their direct comparison (corr-LO > corr-HI).

RESULTS

Behavioral

Reaction time

RT followed a normal distribution (Kolmogorov–Smirnov test for normality, $P > 0.2$, where values above 0.05 indicate no significant difference from the normal distribution). In the full set of trials, there was a significant linear effect of probability on RT to make the decision (unstandardized beta = −10.1, $t = -3.5$, $P = 0.001$; Figure 2A), as would be expected, with decision times slowing as probability for the more likely outcome decreased (i.e. as predictability decreased). There was also a quadratic effect of probability on RT (unstandardized beta = 0.03, $t = 2.1$, $P = 0.04$), indicating the presence of a non-linear relationship. There was an effect of magnitude on RT (unstandardized beta = 12.3, $t = 2.5$, $P = 0.014$), such that high magnitude decisions were associated with faster response times (905.9 ms) compared with low magnitude decisions (930.6 ms). There were no interactions between probability (linear or quadratic effects) and magnitude in RT.

In the RT-restricted data set (secondary analysis), the linear effect of probability on RT was completely eliminated (unstandardized beta = 0.24, $P > 0.4$), allowing for the interrogation of brain activity in relation to predictability in the absence of a significant RT-slowing effect.

Accuracy

Analysis of percent incorrect decisions confirmed that subjects were generally choosing according to probability (linear effect of probability: unstandardized beta = −0.944, $t = -2.3$, $P = 0.02$; Figure 2B). There was also a trend toward an effect of magnitude (unstandardized beta = −1.3, $t = -1.8$, $P = 0.07$), indicating that more incorrect decisions were made for high than low magnitude trials (27.7 *vs* 25.2%). There were no quadratic effects of probability or interactions between probability and magnitude on accuracy.

FMRI

Primary analysis

Results from model 1 indicated that decreasing probability for the more likely outcome (i.e. linear decreases in predictability) for low magnitude decisions (corr-LO) was associated with robust increases in activity in pMFC and bilateral AI (whole-brain analysis, see Table 1 and Figure 3, regions in green). In contrast, for high magnitude decisions (corr-HI) there were no regions showing negative correlations with probability, even in the analysis using an ROI focusing on pMFC and AI. The direct comparison of negative correlations with probability for low as compared to high magnitude decisions (corr-LO > corr-HI) revealed significant activations in pMFC and right AI extending into lateral prefrontal cortex [inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex] (whole-brain analysis, see Table 1 and Figure 3, regions in red). Searching within the ROI confirmed that regions of pMFC and right AI found for the corr-LO > corr-HI contrast overlapped with regions activated for the corr-LO contrast (Figure 3, regions in yellow). However, left AI was not found for corr-LO > corr-HI, and right inferior parietal and posterior temporal activity did emerge from this contrast. Unlike effects for pMFC and right AI, effects in these regions were driven by positive correlations (i.e. increasing probability for the more likely outcome) during high magnitude decisions rather than negative correlations during low magnitude decisions.

Across magnitudes, decreasing probability was associated with greater activity in pMFC and right AI (whole-brain analysis, see

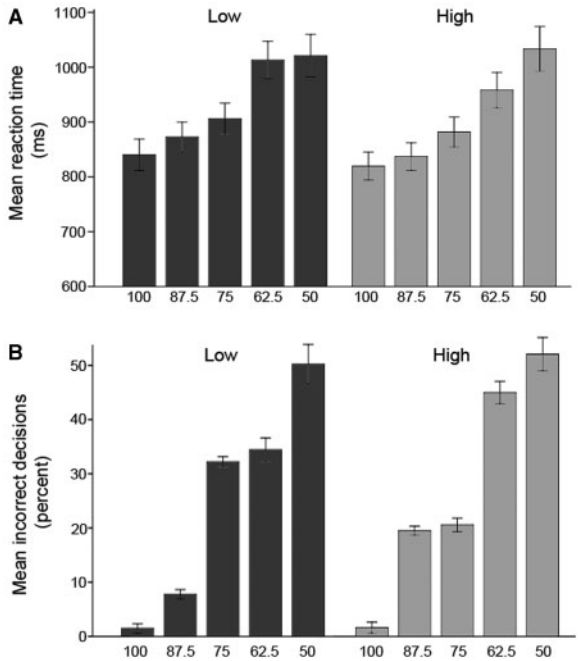

Fig. 2 (**A**) There were linear and quadratic effects of probability and an effect of magnitude on mean RT for correct trials. (**B**) There was a linear effect of probability on percent incorrect decisions. Values on *x*-axis represent % chance for the more likely outcome. Low magnitude decisions: dark gray bars, high magnitude decisions: light gray bars.

Table 1 Negative correlations with probability for the more likely outcome

Contrast/Region (Side)	BA	*k*	*x*	*y*	*z*	Max *Z*
Corr-LO						
pMFC (B)	6, 8, 9, 32	612	10	34	28	5.1
AI (R)	13, 22, 45, 47	137	48	14	−2	3.8
AI (L)	13, 45, 47	159	−44	22	−10	4.2
Corr-LO > corr-HI						
pMFC (B)	9, 32	97	10	42	30	4.0
AI/IFG (R)	10, 13, 45, 46	211	42	30	8	3.9
Inferior parietal (R)	7, 40	473	42	−42	48	4.9
Posterior temporal (R)	20, 21	243	62	−34	−14	4.3
Corr (both magnitudes)						
pMFC (B)	6, 8, 9, 32	248	10	34	24	4.2
AI (R)	13, 22, 45, 47	80	42	16	4	3.8

K, number of voxels; L, left; R, right; B, both hemispheres; coordinates are in MNI space. Corr-LO, negative correlation for low magnitude decisions; corr-HI, negative correlation for high magnitude decisions; corr (both magnitudes), negative correlation for both low and high magnitude decisions.

Table 1); an effect was also found in left AI in the ROI analysis. For the main effect of magnitude (across probability), high magnitude decisions elicited significantly greater activity in occipital cortex than low magnitude decisions (whole-brain analysis, two clusters: $x=4$, $y=-92$, $z=2$, $k=2709$, $Z=5.2$; $x=-30$, $y=-88$, $z=-16$, $k=244$, $Z=4.5$; Brodmann's areas 17, 18, 19, 23). No effects were found in the ROI analysis for high > low magnitude decisions.

To understand the source of the difference in predictability-related pMFC and AI activation for low *vs* high magnitude decisions, parameter estimates (beta weights) for the 10 conditions in Model 2 (all combinations of probabilities and magnitudes) were extracted from the pMFC and right AI/IFG clusters that were found for the corr-LO > corr-HI contrast (Figure 4A) as well as the three clusters found for the corr-LO contrast (Figure 4B). Note that we expect to find a differential relationship with probability for low compared with high magnitude decisions, as parameter estimates were obtained from regions in pMFC and AI derived from a contrast specifically probing this differential relationship. However, inspection of these parameter estimates provides insight into the overall pattern of the data, revealing that higher probability decisions (i.e. those with greater predictability, 100%, 87.5% and/or 75%) showed relatively more activity for high magnitude (Figure 4, light gray bars) than low magnitude (Figure 4, dark gray bars) decisions. This finding is exploratory and must be interpreted with caution, as pMFC and AI ROIs were derived from the same data set as the parameter estimates shown in Figure 4 (see Kriegeskorte *et al.*, 2009). Future analyses using independent data sets for ROIs and extracted parameter estimates will be needed to confirm this pattern.

Secondary analysis—RT restricted

Consistent with prior literature (Grinband *et al.*, 2006; Krain *et al.*, 2006; Stern *et al.*, 2010; Daniel *et al.*, 2011), our behavioral results found a negative linear relationship between probability for the more likely outcome and RT in the full data set. Although work in the field would suggest that this RT effect is due to a direct relationship between the inability to predict an outcome and slowed responses to make that prediction, it is also possible that RT slowing could be due to non-specific effects related to difficulty, attention or arousal. If this were the case, it is possible that some portion of brain activity correlated with probability in our primary analyses could actually be related to these non-specific RT-slowing effects.

In the RT-restricted data set where the slowing effect was eliminated, there were no significant effects for corr-LO or corr-HI in whole-brain analysis. However, ROI analyses revealed that all three regions found

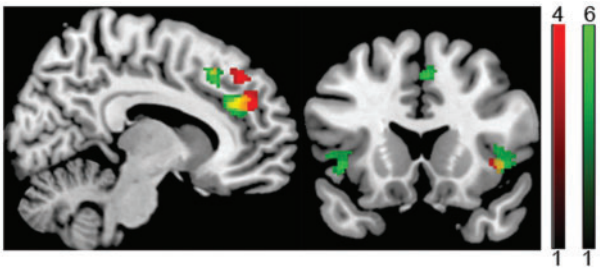

Fig. 3 Greater pMFC and AI activation for the corr-LO (green) and corr-LO > corr-HI (red) contrasts (overlap in yellow).

for corr-LO in the full dataset were also found in the restricted data set, including pMFC [three clusters: $x=10$, $y=38$, $z=28$, $k=140$, $Z=4.0$; $x=8$, $y=40$, $z=42$, $k=58$, $Z=3.8$; $x=-8$, $y=28$, $z=44$, $k=124$, $Z=3.5$, Brodmann's areas (BAs) 6, 8, 9, 32], right AI (one cluster: $x=42$, $y=26$, $z=-12$, $k=39$, $Z=3.2$, BA 47) and left AI (two clusters: $x=-48$, $y=20$, $z=2$, $k=24$, $Z=3.5$; $x=-40$, $y=24$, $z=-14$, $k=35$, $Z=3.1$, BAs 45, 47). The ROI analysis did not yield any effects for corr-HI in the restricted data set. Accordingly, the ROI analysis of the direct contrast of corr-LO > corr-HI revealed activation in pMFC ($x=12$, $y=40$, $z=26$, $k=25$, $Z=3.2$, BAs 9, 32) and right AI/IFG (two clusters: $x=32$, $y=12$, $z=-10$, $k=27$, $Z=3.1$; $x=30$, $y=40$, $z=-14$, $k=68$, $Z=3.6$, BAs 11, 13, 47). In the whole-brain analysis, corr-LO > corr-HI again revealed regions of right inferior parietal ($x=44$, $y=-46$, $z=38$, $k=172$, $Z=4.0$, BA 40) and posterior temporal cortex ($x=60$, $y=-44$, $z=-13$, $k=95$, $Z=4.2$, BA 37) that showed positive correlations with probability on high magnitude decisions. Overall, these data indicate that the relationship between decreasing probability (i.e. decreasing predictability) and pMFC and AI activation is present (although weakened) when eliminating the association with RT.

Secondary analysis—variance

In the analysis where low and high magnitude decisions were modulated by the quadratic variance measure, we were intrigued to find results largely overlapping with that obtained from the primary model using the linear probability measure. In whole-brain analyses, both pMFC ($x=-2$, $y=28$, $z=42$, $k=535$, $Z=4.7$, BAs 6, 8, 9, 32) and left AI ($x=-44$, $y=22$, $z=-12$, $k=121$, $Z=3.8$, BAs 13, 45, 47) were significantly related to increasing variance for low magnitude decisions (corr-LO), with right AI ($x=48$, $y=14$, $z=-2$, $k=81$, $Z=3.7$, BAs 13, 45, 47) emerging at trend level (whole-brain corrected $P=0.059$). No regions were correlated with variance for high magnitude decisions (corr-HI), even in the ROI analysis, and direct whole-brain comparisons (corr-LO > corr-HI) yielded significant effects in pMFC ($x=-2$, $y=28$, $z=42$, $k=537$, $Z=4.7$, BAs 6, 8, 9, 32) and left AI ($x=-44$, $y=22$, $z=-12$, $k=124$, $Z=3.9$, BAs 13, 45, 47). Right AI emerged for this contrast just below corrected threshold ($x=48$, $y=14$, $z=-2$, $k=79$, $Z=3.6$, BAs 13, 45, 47, whole-brain corrected $P=0.068$).

DISCUSSION

This study investigated neural responses in pMFC and AI when subjects made decisions associated with varying outcome predictability and magnitude. While many studies have reported greater activity in these regions with decreasing predictability (as measured by probability or variance), prior research has not investigated whether this relationship is impacted by the magnitude or 'stakes' of the decision. An investigation of the way magnitude affects neural responses to

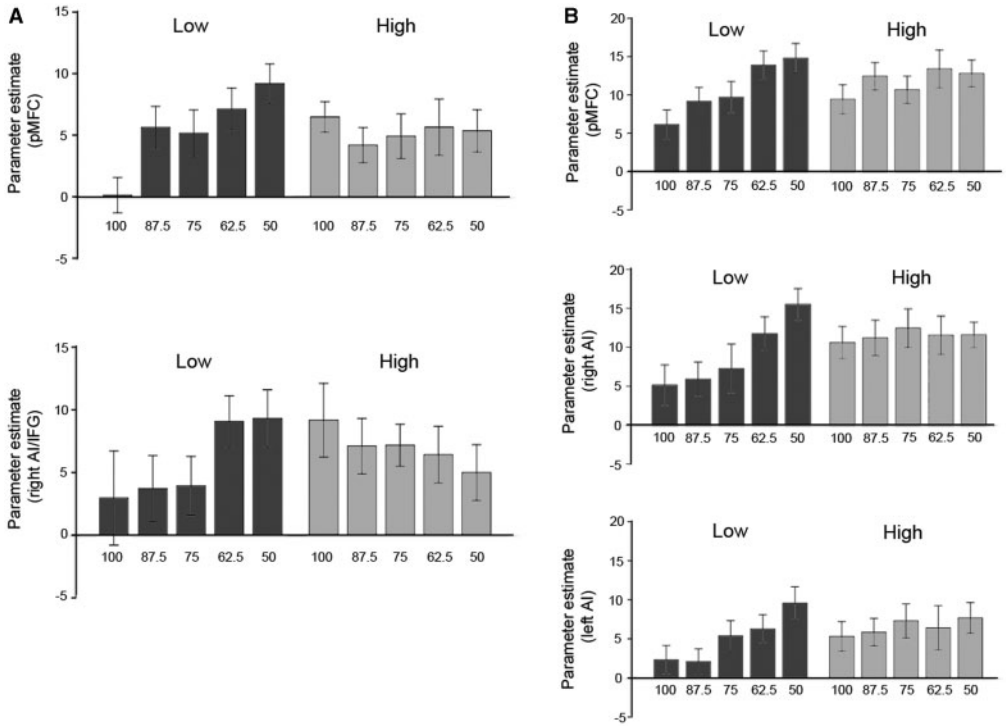

Fig. 4 (**A**) Mean parameter estimates for each probability and magnitude in regions of pMFC and right AI/IFG found for the corr-LO > corr-HI contrast; (**B**) mean parameter estimates for regions of pMFC, right AI and left AI found for the corr-LO contrast. Values on *x*-axis represent % chance for the more likely outcome. Low magnitude decisions: dark gray bars, high magnitude decisions: light gray bars.

predictability may help inform dysfunctional decision making in psychiatric disorders characterized by altered perceptions of likelihood for high stakes negative outcomes, such as obsessive-compulsive disorder (Steketee *et al.*, 1998; Sookman and Pinard, 2002). Results from the current experiment indicated that pMFC and AI are modulated by outcome predictability (both in terms of probability and variance) for low but not high stakes decisions.

When making relative low stakes decisions, pMFC and AI showed greater activity as predictability of the outcome decreased, replicating several prior studies (Critchley *et al.*, 2001; Paulus *et al.*, 2002; Volz *et al.*, 2003; Huettel *et al.*, 2005; Krain *et al.*, 2006; Tobler *et al.*, 2007; Preuschoff *et al.*, 2008; Stern *et al.*, 2010). However, these regions were not sensitive to outcome predictability for high stakes decisions. These data indicate that pMFC and AI are not simply tracking predictability related to probability or variance. Instead, the results suggest a more complex relationship whereby predictability is processed linearly (or quadratically) when the stakes are relatively low, but that high and low predictability are not similarly distinguished for higher stakes decisions. It has recently been suggested that pMFC and AI form a general 'salience network' responsible for detecting important information to trigger further processing (Seeley *et al.*, 2007; Sridharan *et al.*, 2008). A general function for pMFC and AI is supported by the wide range of paradigms eliciting activity in these brain regions, including emotion (Kober *et al.*, 2008), interoception (Critchley *et al.*, 2004), conflict and error processing (van Veen *et al.*, 2001; Taylor *et al.*, 2007; Pochon *et al.*, 2008) and attention switching (Wager *et al.*, 2004). In this study, faster RTs for high stakes decisions suggests that they were indeed more salient. The lack of relationship between predictability and pMFC and AI activation for high stakes decisions lends further support for the notion that these brain regions respond to salient information, of which outcome predictability is just one contributing factor. However, it must be noted that one might expect the salience associated with the decision to increase as predictability decreased within high magnitude decisions. Although speculative, it is possible there was an upper boundary either for the salience elicited by decisions in the task, or for the BOLD signals in pMFC and AI, that was reached on high stakes decisions.

Behavioral data indicated that probability was related to RT to make the decision, as would be expected given the increased processing time required for decision making when the outcome is less predictable. However, given that cognitive events other than predictability could also lead to slowed response times, such as general effort, attention or arousal, we analyzed the relationship between predictability and pMFC and AI activity within a restricted data set that eliminated this relationship. In this restricted analysis, we found that activity in these regions was still related to probability on low stakes decisions even when the RT-slowing effect was completed eliminated. Even though the overall strength of the relationship was reduced as compared with results from the full data set, it is likely that this is attributable to the reduced power of the RT-restricted analysis due to the removal of ~1/3 of trials in the experiment. However, it is also possible that some portion of the identified activity in the full dataset is indeed related to RT slowing, and future studies will be needed to understand the relationship between non-specific RT effects and pMFC and AI activity.

Limitations of this study suggest avenues for future research. First, we employed five levels of probability to examine predictability, but only two different magnitudes. It would be interesting to use several different magnitudes to determine more precisely at what point the typical negative correlations between predictability and pMFC and AI activation weaken. In addition, although we believe these findings are relevant for understanding altered decision making in psychiatric disorders, a more definitive link would be obtained by directly investigating the relationship between brain activity in this task and trait measures of intolerance of uncertainty and risk overestimation (see Krain *et al.*, 2008). Despite these limitations, results from this study

indicate that the relationship between outcome predictability and pMFC and AI activity depends on the stakes of the decision. This novel finding lends support for the involvement of a salience network that responds to multiple decision variables signaling importance.

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