SUPPLEMENTAL INFORMATION

The functional roles of the amygdala and prefrontal cortex in processing uncertainty

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Healthy controls: Gambling behavior as a function of uncertainty type. Dovetailing with previous work (Levy, Snell et al. 2010, Tymula, Belmaker et al. 2012, FeldmanHall, Glimcher et al. 2016), Healthy Controls (HCs; N=40) gambled less when the lotteries were ambiguous, compared to when they were risky (Fig S1). Participants gambled the most—61% of the time—when the trial was risky and there was a high probability of winning (75% chance, Fig S1A). As the gamble became riskier, and the chances of winning declined, participants were less likely to take the gamble, decreasing their gambling rate to 24% when there was only a 25% chance of winning.

To confirm whether ambiguous uncertainty has an effect on choice behavior (Glimcher 2008, Levy, Snell et al. 2010, Tymula, Belmaker et al. 2012), we explored the rates at which participants gambled during ambiguous trials compared to risky trials. In line with the idea that ambiguous uncertainty is more aversive than risky uncertainty, ambiguous trials were treated as if the winning probability was less than 50% (Fig S1B). While participants gambled on 56% of trials where there was a known 50/50 chance of winning (50% risk, indicated by the dotted line in Fig S1A), they took significantly less gambles during trials that contained large amounts of ambiguity. During ambiguous trials, even though increasing the occluder size reduces information about the lottery, the objective winning probability is always 50%. This is because red chips are the winning color in exactly half of the trials, and participants do not know whether a red or blue chip will be selected for play (Ellsberg 1961, Glimcher and Rustichini 2004). Despite this, results reveal that gambling rates decreased as a function of increasing ambiguity, suggesting that not only do individuals perceive ambiguity as more aversive than risk, but that greater ambiguity is mirrored by an increasing reticence to gamble (Fig S1B).

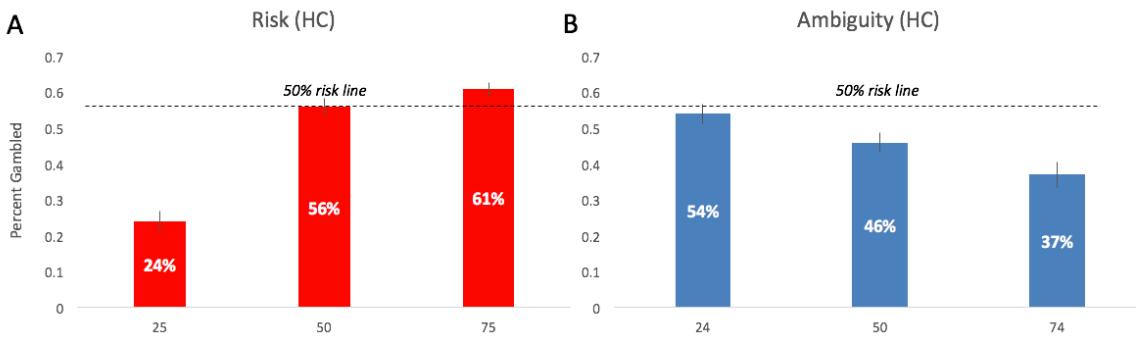

Fig S1 | Gambling behavior for healthy controls (HCs). A) *Participants gambled the most when the trial contained risky uncertainty and there was a high likelihood (75%) of winning. As the lottery became riskier (25% chance of winning), participants were less likely to gamble (24% endorsement rate).* ***B)*** *Ambiguous uncertainty is perceived as more aversive than risky uncertainty: All ambiguous trials were treated as if the winning probability were less than 50%. Gambling rates at 50% risk is indicated by the dotted reference line.*

These findings were also found using the risk and ambiguity attitudes derived from the model. HCs exhibited predictably high risk aversion, denoted by 90% of subjects falling below the neutral risk line (mean α=.56 SD±.24; Fig S2A) and ambiguity aversion, denoted by 82% of subjects falling below the neutral ambiguity line (mean β=.37 SD±.56: Fig S2B). Moreover, in line with our prior research (FeldmanHall, Glimcher et al. 2016), there was no relationship between risk and ambiguity attitudes at the population level (Pearson's r=0.13, p=0.42: Fig S2C).

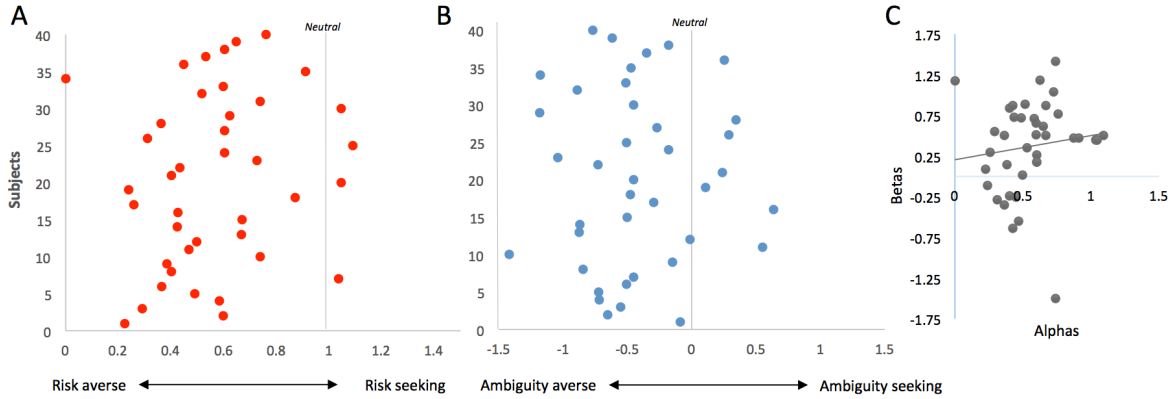

Fig S2 | *Healthy Controls' Risk* ***(A)*** *and ambiguity attitudes* ***(B)****. The dotted line indicates attitudes that are risk or ambiguity neutral. Betas were inverted to be on the same scale as alphas.* ***C)*** *Correlating betas and alphas at the population level revealed no significant relationship.*

Healthy controls: Emotional arousal and choice. To examine the relationship between subjective value and arousal, we ran a trial-by-trial mixed effects hierarchal linear regression that modeled Skin Conductance Response (SCR) as a function of every trial's subjective value given a

participant's risk and ambiguity attitudes (Table S1). Results reveal a main effect of subjective value predicting SCR, such that greater subjective value correlated with increasing SCR. The fact that we observed a relationship between how much an individual subjectively values a lottery and their arousal response suggest that there should also be a relationship between choosing to gamble and arousal levels. Evidence supports this for decisions made under risk and ambiguity (Tables S2-S3). When the choice was highly risky, higher arousal levels signaled that the gamble should not be taken (Table S2). However, when the choice was ambiguous, higher arousal predicted decisions to gamble (Table S3).

TABLE S1 | HC: $SCR_{i,t} = \beta_0 + \beta_1 Subjective\ Value_{i,t}$
SCR ~ SV; where SCR and SV is indexed by subject and trial.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
SCR	Intercept	*0.39 (.05)*	*7.05*	*<0.001****
	SV	*0.002 (.001)*	*2.10*	*0.03**

***p<0.001, **p<0.01, *p<0.05

TABLE S2 | HC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}\,(Risk25\%_{i,t}) + \beta_2 SCR_{i,t}\,(Risk50\%_{i,t}) + \beta_3 SCR_{i,t}\,(Risk75\%_{i,t})$
Choice ~ SCR X Risk Level; where SCR and Risk level is indexed by subject and trial and each level of Risk level is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*-0.06 (.08)*	*-0.79*	*0.25*
	SCR X Risk 25%	*-1.40 (.33)*	*-4.21*	*<0.001****
	SCR X Risk 50%	*0.18 (.20)*	*0.91*	*0.36*
	SCR X Risk 75%	*.35 (.18)*	*1.95*	*0.051^*

***p<0.001, **p<0.01, *p<0.05

TABLE S3 | HC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}(Amb25\%_{i,t}) + \beta_2 SCR_{i,t}(Amb50\%_{i,t}) + \beta_3 SCR_{i,t}(Amb75\%_{i,t})$
Choice ~ SCR X Ambiguity Level; where SCR and Ambiguity level is indexed by subject and trial and each level of Ambiguity is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*-0.21 (.16)*	*-1.31*	*0.20*
	SCR X Ambiguity 25%	*0.56 (.24)*	*2.32*	*0.02**
	SCR X Ambiguity 50%	*0.61 (.24)*	*2.50*	*0.01**
	SCR X Ambiguity 75%	*0.08 (.28)*	*0.30*	*0.76*

***p<0.001, **p<0.01, *p<0.05

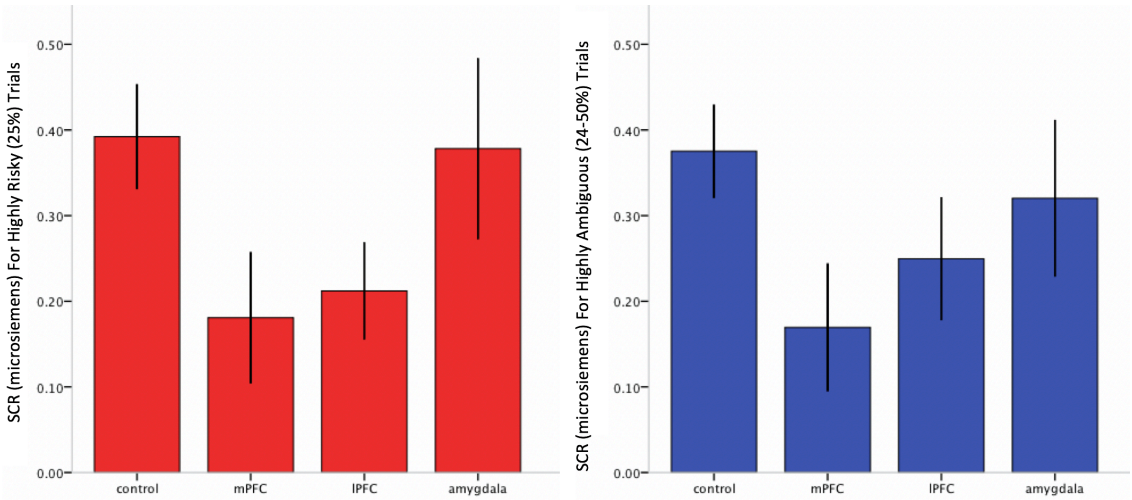

Fig S3 | Skin conductance responses during gambles for all groups. A) *Arousal levels for highly risky gambles and* ***B)*** *ambiguous gambles reveals that the control group has higher arousal levels then the other patient groups, however, the ANOVA failed to reach significance. Bars reflect 1 standard error of the mean.*

Patients: Emotional arousal and choice. This relationship—for both risk and ambiguity—was abolished in the lPFC group, revealing that arousal did not act as an inhibitory or excitatory signal under either type of uncertainty (Table S4-S5). Both the mPFC and amygdala group exhibited an intact relationship between high arousal and choices to refrain from gambling on the highly risky trials (Tables S6-S8). However, neither group exhibited an intact relationship between high arousal and decisions to engage in ambiguous gambles (Tables S7-S9), which was observed in the HCs.

TABLE S4 | lPFC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}\,(Risk25\%_{i,t}) + \beta_2 SCR_{i,t}\,(Risk50\%_{i,t}) + \beta_3 SCR_{i,t}\,(Risk75\%_{i,t})$

Choice ~ SCR X Choice ~ SCR X Risk level; where SCR and Risk level is indexed by subject and trial and each level of Risk level is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*0.07 (.22)*	*0.32*	*0.75*
	SCR X Risk 25%	*0.34 (.58)*	*0.58*	*0.55*
	SCR X Risk 50%	*0.58 (.67)*	*0.86*	*0.38*
	SCR X Risk 75%	*-0.01 (.67)*	*-0.02*	*0.98*

***p<0.001, **p<0.01, *p<0.05

TABLE S5 | lPFC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}(Amb25\%_{i,t}) + \beta_2 SCR_{i,t}(Amb50\%_{i,t}) + \beta_3 SCR_{i,t}(Amb75\%_{i,t})$

Choice ~ SCR X Choice ~ SCR X Ambiguity Level; where SCR and Ambiguity level is indexed by subject and trial and each level of Ambiguity is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*0.11 (.30)*	*0.38*	*0.70*

	SCR X Ambiguity 25%	*1.30 (1.2)*	*1.04*	*0.29*
	SCR X Ambiguity 50%	*-0.25 (.82)*	*-0.31*	*0.75*
	SCR X Ambiguity 75%	*-0.33 (.55)*	*-0.59*	*0.55*

***p<0.001, **p<0.01, *p<0.05

TABLE S6 | mPFC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}\,(Risk25\%_{i,t}) + \beta_2 SCR_{i,t}\,(Risk50\%_{i,t}) + \beta_3 SCR_{i,t}\,(Risk75\%_{i,t})$

Choice ~ SCR X Risk Level; where SCR and Risk level is indexed by subject and trial and each level of Risk level is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*-0.13 (.23)*	*-0.55*	*0.58*
	SCR X Risk 25%	*-2.57 (.82)*	*-3.13*	*0.001****
	SCR X Risk 50%	*2.42 (1.5)*	*1.60*	*0.11*
	SCR X Risk 75%	*0.75 (.81)*	*0.93*	*0.35*

***p<0.001, **p<0.01, *p<0.05

TABLE S7 | mPFC: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}(Amb25\%_{i,t}) + \beta_2 SCR_{i,t}(Amb50\%_{i,t}) + \beta_3 SCR_{i,t}(Amb75\%_{i,t})$

Choice ~ SCR X Ambiguity Level; where SCR and Ambiguity level is indexed by subject and trial and each level of Ambiguity is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*-0.31 (.35)*	*-0.87*	*0.38*
	SCR X Ambiguity 25%	*0.32 (1.2)*	*0.28*	*0.79*
	SCR X Ambiguity 50%	*0.13 (.88)*	*0.15*	*0.88*
	SCR X Ambiguity 75%	*-0.03(.69)*	*-0.04*	*0.97*

***p<0.001, **p<0.01, *p<0.05

TABLE S8 | Amygdala: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}\,(Risk25\%_{i,t}) + \beta_2 SCR_{i,t}\,(Risk50\%_{i,t}) + \beta_3 SCR_{i,t}\,(Risk75\%_{i,t})$

Choice ~ SCR X Risk Level; where SCR and Risk level is indexed by subject and trial and each level of Risk level is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*0.01 (.213)*	*0.08*	*0.93*
	SCR X Risk 25%	*-3.17 (1.02)*	*-3.11*	*0.002**
	SCR X Risk 50%	*0.28 (467)*	*0.62*	*0.53*
	SCR X Risk 75%	*0.39 (.36)*	*1.10*	*0.27*

***p<0.001, **p<0.01, *p<0.05

TABLE S9 | Amygdala: $Choice_{i,t} = \beta_0 + \beta_1 SCR_{i,t}(Amb25\%_{i,t}) + \beta_2 SCR_{i,t}(Amb50\%_{i,t}) + \beta_3 SCR_{i,t}(Amb75\%_{i,t})$

Choice ~ SCR X Ambiguity Level; where SCR and Ambiguity level is indexed by subject and trial and each level of Ambiguity is an indicator variable.

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
Choice	Intercept	*-0.33 (.24)*	*-1.38*	*0.17*
	SCR X Ambiguity 25%	*-0.18 (.75)*	*-0.24*	*0.80*
	SCR X Ambiguity 50%	*0.04 (.49)*	*0.08*	*0.93*
	SCR X Ambiguity 75%	*-2.23 (1.24)*	*-1.79*	*0.073^*

***p<0.001, **p<0.01, *p<0.05

Patients: Risk and Ambiguity attitudes. Patients individual risk (Fig S4a) and ambiguity (Fig S4b) attitudes—which are obtained from the behavioral fit of the model (our model did an excellent job of correctly predicting subjects' [both HCs and patient groups] choices, see Table S12 below; however it should be noted that this analysis relies on the accuracy of the parametric model of human choice behavior we chose to employ and thus may reflect idiosyncrasies of the model)—are plotted below. Average risk and ambiguity attitudes for HCs are indexed by the red and blue lines respectively, where shaded bars denote 1SEM. Risk and ambiguity neutral lines are denoted by the dotted line. We found no relationship between risk and ambiguity attitudes at the population level for mPFC patients (Pearson's r=0.37, p=0.32), lPFC patients (Pearson's r=0.52, p=0.18), or amygdala patients (Pearson's r=0.18, p=0.49).

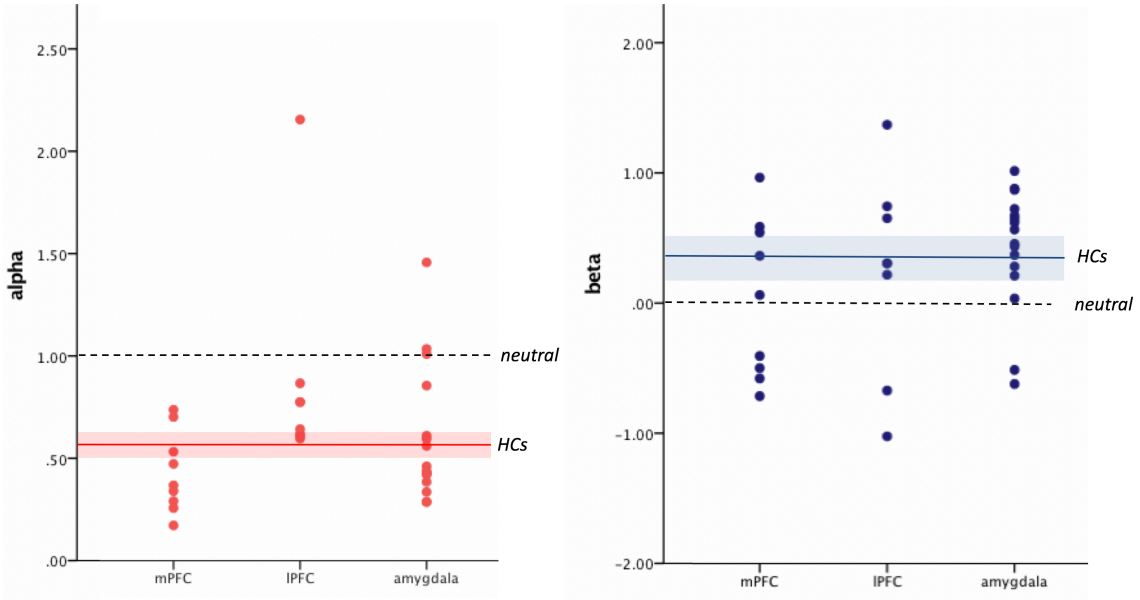

Fig S4 | *Patient's Risk* ***(A)*** *and ambiguity attitudes* ***(B)****. The dotted line indicates attitudes that are risk or ambiguity neutral.*

Model Based Attitudes Toward Uncertainty. To examine how lesions to the lPFC, mPFC, and amygdala effect attitudes towards uncertainty, we took each individual's risk (α) and ambiguity (β) attitudes, and ran a one-way ANOVA that included all patient groups as well as HCs. This allows us to directly test for differences in attitudes towards uncertainty for each lesion group against HCs, while simultaneously examining whether each group is impaired in the processing of risk and ambiguity relative to all other groups.

The ANOVA for risk attitudes (DV=Alpha [α], IV=Lesion group) illustrated significant differences between lesion groups (F(3,72)=2.80, p=0.045; Fig S4A). Post hoc LSD tests revealed that individuals with lesions to the lPFC had higher risk attitudes (mean α=0.89 SD±.57) compared to HCs (α=.57 SD±.24: P=0.01), mPFC patients (mean α=0.48 SD±.23; P=0.008), and unilateral amygdala patients (mean α=.61 SD±.33; P=0.042). In other words, lPFC patients exhibited significantly greater risk-seeking compared to the HCs and all the other patient groups.

The same ANOVA with ambiguity attitudes (DV=Beta [β], IV=Lesion group) demonstrated no differences at the group level (F(3,72)=1.9, p=0.13; Fig S4B); however, post hoc LSD tests revealed that those with lesions to the mPFC had significantly greater ambiguity seeking behavior (mean β=-0.058 SD±.66) compared to HCs (mean β=0.37 SD±.55; P=0.033), which stands in contrast to prior research (Hsu et al's reported activity and damage in lOFC (51, 33, -6) overlaps with five out of eight lPFC patients in our sample; Hsu, Bhatt et al. 2005). Patients with mPFC damage were also more tolerant of ambiguity compared to those with unilateral amygdala lesions (mean β=.43 SD±.46; P=0.035); differences between mPFC and lPFC groups were in the same direction, but were marginal (mean β=0.43 SD±.62; P=0.08).

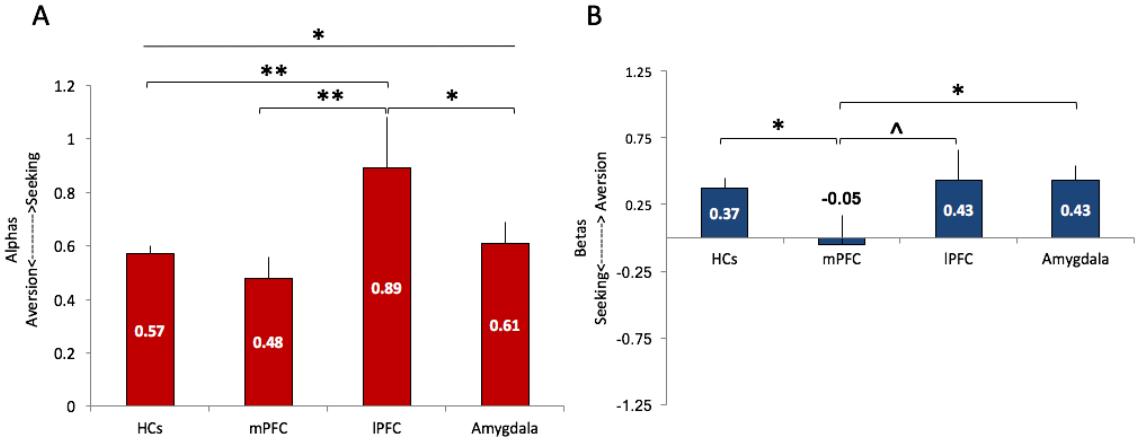

FIG S5 | Risk and ambiguity attitudes derived from the model. A) Risk Attitudes. *Compared to HCs, patients with lesions to the lPFC exhibited a significant increase in their willingness to gamble.* ***B) Ambiguity attitudes.*** *Compared to HCs, and all other patient groups, patients with lesions to the mPFC exhibited an increase in their ambiguity tolerance (i.e. mPFC patients were more ambiguity seeking). Error bars reflect 1 standard error of the mean.*

TABLE S10 | Summary Table of Model Free and Model Based Results for Risky choices

	HC	*mPFC*	*lPFC*	*Amygdala*
Model Free (raw choice)		No relationship between damage and choice	Greater damage leads to increased risk taking	No relationship between damage and choice
Model Based (model derived attitudes)		No difference from HC	Significantly greater risk seeking attitudes than HC	No difference from HC
SCR	Higher SCR linked with *decreased* gambling	Higher SCR linked with *decreased* gambling (not significantly different from HC) for very risky choices	Higher SCR linked with *increased* gambling (significantly more so than HCs) for very risky choices	Higher SCR linked with *decreased* gambling (not significantly different from HC) for very risky choices

Summary Table of Model Free and Model Based Results for Ambiguous decisions

	HC	*mPFC*	*lPFC*	*Amygdala*
Model Free (raw choice)		No relationship between damage and choice	Greater damage leads to increased ambiguity taking	No relationship between damage and choice
Model Based (model derived attitudes)		Significantly greater ambiguity seeking attitudes than HC	No difference from HC	No difference from HC
SCR	Higher SCR linked with *increased* gambling	Higher SCR linked with *decreased* gambling (not significantly different from HC)	Higher SCR linked with *decreased* gambling (not significantly different from HC)	Higher SCR linked with *decreased* gambling (not significantly different from HC)

Patients: Emotional arousal and subjective value. To examine the relationship between subjective value and arousal in the patient groups, we ran a trial-by-trial mixed effects hierarchal linear regression that modeled SCR as a function of every trial's subjective value given a participant's risk and ambiguity attitudes (Table S11). This allowed us to test whether each patient group exhibited a similar positive relationship between subjective value and affect that we observed in HCs. Results from the lPFC group revealed the opposite relationship, such that increasing subjective value led to decreasing arousal levels. In contrast, neither the mPFC or amygdala group had any intact relationship between arousal and subjective value.

TABLE S11| Subjective Value Predicts Arousal: All patient groups

$SCR_{i,t} = \beta_0 + \beta_1\ Subjective\ Value_{i,t}(Lesion\ Type)$

SCR ~ SV; where SCR and SV is indexed by subject and trial and Lesion is an indicator variable

Dependent Variable	***Coefficient*** $(\boldsymbol{\beta})$	***Estimate (SE)***	***t-value***	***P value***
SCR	Intercept	*0.32 (.03)*	*8.92*	*<0.001****

	mPFC X SV	*0.001 (.002)*	*0.51*	*0.61*
	lPFC X SV	*-0.0001 (.0005)*	*-2.46*	*0.01***
	Amygdala X SV	*0.0002 (.0001)*	*-0.12*	*0.90*

***p<0.001, **p<0.01, *p<0.05

Model Data for All Groups

Model descriptives. Below we report the average risk and ambiguity attitudes for each group, as well as the range of attitudes.

TABLE S12: Population level descriptives of model parameters.

	Mean	SD	Min	Max
HC Alphas	0.57	.24	.22	1.04
HC Betas	0.37	.55	-1.50	1.18
lPFC Alphas	0.89	.57	.61	2.18
lPFC Betas	0.43	.62	-.66	1.38
mPFC Alphas	0.48	.23	.17	.87
mPFC Betas	-0.058	.66	-1.02	.98
amygdala Alphas	0.61	.33	.29	1.47
amygdala Betas	0.43	.46	-0.61	.88

Model Fits. To get an overall sense of how well our model fits choice behavior, we calculated the percentage of choices that are correctly predicted by the model. We first calculated the subjective value of the lottery and compared it to the subjective value of the reference choice (always $5). If the subjective value of the lottery is higher than the subjective value of the reference choice, then our model indicates the participant should choose the lottery and not the reference choice. We compared the number of times the model correctly predicted choice based on these criteria. Our model predicts choice extremely well (Tables S13). In only six subjects did the model fail to correctly predict choice at least 80% of the time.

TABLE S13:

Percentage of choice correctly predicted by model	Mean	SD	Min	Max
HC % of choices correctly predicted by model	87.4%	.12	38%	100%
lPFC % of choices correctly predicted by model	90.0%	.06	79%	97%
mPFC % of choices correctly predicted by model	85.0%	.07	75%	94%
Amygdala % of choices correctly predicted by model	89.0%	.05	77%	98%

Supplemental Methods

Task. Participants completed a computerized lottery task consisting of 62 trials, adapted from Tymula and colleagues (Tymula et al., 2012). Each lottery depicted a stack of 100 red and blue poker chips. The lotteries corresponded to actual bags filled with red and blue chips placed in the testing lab and which were used to pay participants (see the table below for full list of choice types, which were evenly presented across the task, 3.2% choice proportions). The color associated with winning the monetary reward was counterbalanced, as was the side the lottery option was presented.

RISK	***AMBIGUITY***
Risk 25% $5	Ambiguity 24% $5
Risk 25% $8	Ambiguity 24% $8
Risk 25% $20	Ambiguity 24% $20
Risk 25% $50	Ambiguity 24% $50
Risk 25% $125	Ambiguity 24% $125
Risk 50% $5	Ambiguity 50% $5
Risk 50% $8	Ambiguity 50% $8
Risk 50% $20	Ambiguity 50% $20
Risk 50% $50	Ambiguity 50% $50
Risk 50% $125	Ambiguity 50% $125
Risk 75% $5	Ambiguity 74% $5
Risk 75% $8	Ambiguity 74% $8
Risk 75% $20	Ambiguity 74% $20
Risk 75% $50	Ambiguity 74% $50
Risk 75% $125	Ambiguity 74% $125

Regions of Interest Masks

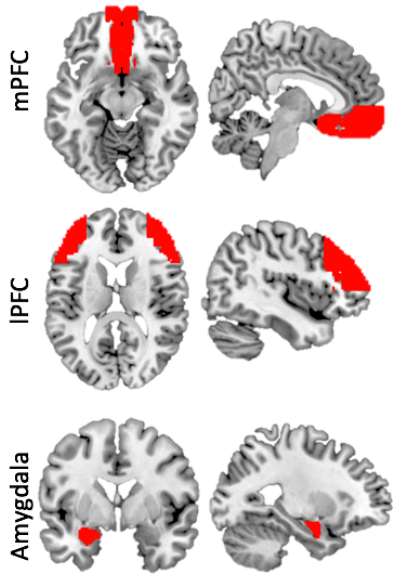

Fig S6 | Region of Interest Masks. *Region of interest (ROIs) masks were constructed with MarsBar toolbox by combining corresponding structures from the Harvard-Oxford Maximum Probability Atlases. The mPFC ROI consisted of the frontal pole, frontal medial cortex, paracingulate gyrus, subcallosal cortex. The lPFC ROI consisted of the inferior frontal gyrus, middle frontal gyrus. Finally, amygdala ROIs were created using the Harvard-Oxford Subcortical Atlas thresholded at 25% probability.*

Supplemental References

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