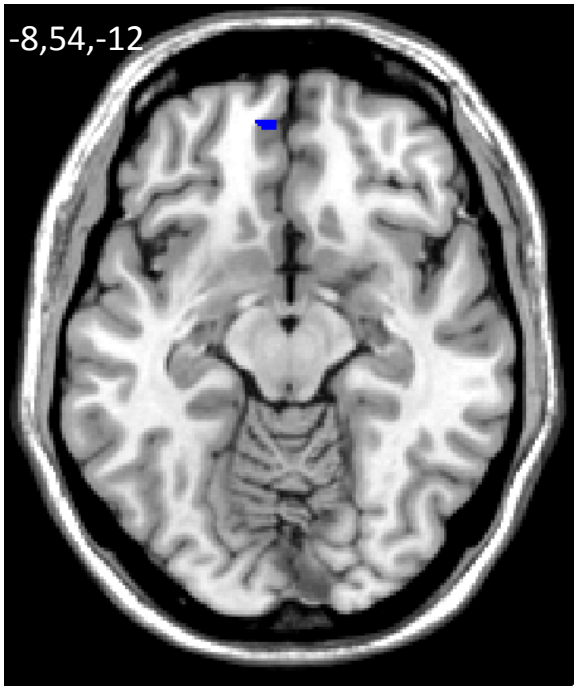
Supplementary material

Other potential sources of reward magnitude information: medial OFC

In our analysis of the potential origin of signals carrying information about reward magnitude to ACC, we used DCM to model causal relationships between ACC and areas showing a main effect of reward magnitude. While previous work has identified medial orbitofrontal cortex (MOFC) as a region which is sensitive to expected value (Knutson, Taylor et al., 2005), we failed to findan effect of reward magnitude in our main analyses. However, in order to rule out the possibility that ACC receives reward magnitude information from MOFC, we conducted an ROI analysis, using an anatomically predefined area covering left and right MOFC. A region showing significant effects of reward magnitude was found with a peak activation at -8, 54, -12 ($t(23)=4.1$, $p<0.01$ uncorrected; figure S1).

Figure S1. Medial OFC region.



This region was used in a second set of DCM analyses which attempted to characterize the causal relationships between MOFC and other areas showing a main effect of reward magnitude or implicated in the processing of reward information. These analyses were conducted in the same manner as described in the main text, and the full results of all analyses are displayed in table S1.

While an optimal model was selected for each of the potential pairwise relationships investigated, these findings are debased by the low parameters estimates found for these models. No significant modulation of connectivity by levels of reward magnitude was found for any model involving MOFC, and estimates of intrinsic connectivity were not significantly different from zero. An in important consideration in the present analyses is that the Bayesian model selection algorithm does not require a model to be a good description of the system being modeled, only that the model performs better than alternative models. The pairwise models used in the DCM analyses may be inappropriate for capturing the functional connectivity between MOFC and other brain areas, and that a single model exceeded the threshold may simply indicate that it is less bad than the alternative models.

Correlation of ACC with areas coding reward magnitude

A preliminary step in our investigation of potential sources of reward magnitude signals to ACC was to examine the correlation of activity of ACC with that of brain areas showing effects of reward magnitude as a necessary, though not sufficient condition for causality. Average reward is calculated as the sum of the gain (or loss) for all potential outcomes multiplied by the probability that each outcome will occur. In the change-signal task, the average reward is highest for trials with high reward magnitude and low error likelihood (High RM/ Low EL) and lowest for trials with low reward magnitude and high error likelihood (Low RM/ High EL). We used this more extreme contrast in the following correlation analyses for maximum sensitivity. Percent signal change of this extreme contrast were extracted from the three ROIs (figure 4, main text) that showed main effects of reward magnitude. These regions had been identified earlier using the main effect contrast of High RM- Low RM, as described in the main text. We also extracted the percent signal change for the extreme contrast from the ACC ROI (figure S2). In all cases, percent signal change was calculated from the averaged activity of all voxels in an ROI which exceeded a threshold of $p<0.01$. A correlation across subjects was conducted between ACC and each of the regions showing a main effect of reward magnitude using the contrast High RM/Low EL – Low RM/High EL**.** Two of these regions showed a significant positive correlation with ACC (figure S2): increased activity in IFG correlated with increased activity in ACC ($r=0.498$, $p<0.05$), as did activity in PH ($r=0.550$, $p<0.01$). Activity in VStr showed a trend toward a positive correlation, but missed significance

(r=0.3773, p=0.076). The areas identified in the present study as being sensitive to reward magnitude are consistent with previous work showing multiple areas in the brain sensitive to reinforcement learning tasks. Activity in PH has been observed to correlate positively with the probability of receiving a reward (Knutson, Taylor et al., 2005). Rolls and colleagues (Rolls, McCabe et al., 2008) observed a correlation between activity in IFG and reward prediction-related temporal difference errors, while activity in VStr corresponds with the level of context-dependent financial rewards (Elliott, Friston et al., 2000). Activity in these areas could in principle be the source of reward magnitude signals to ACC, but this remains to be tested more directly below in the section on DCM.

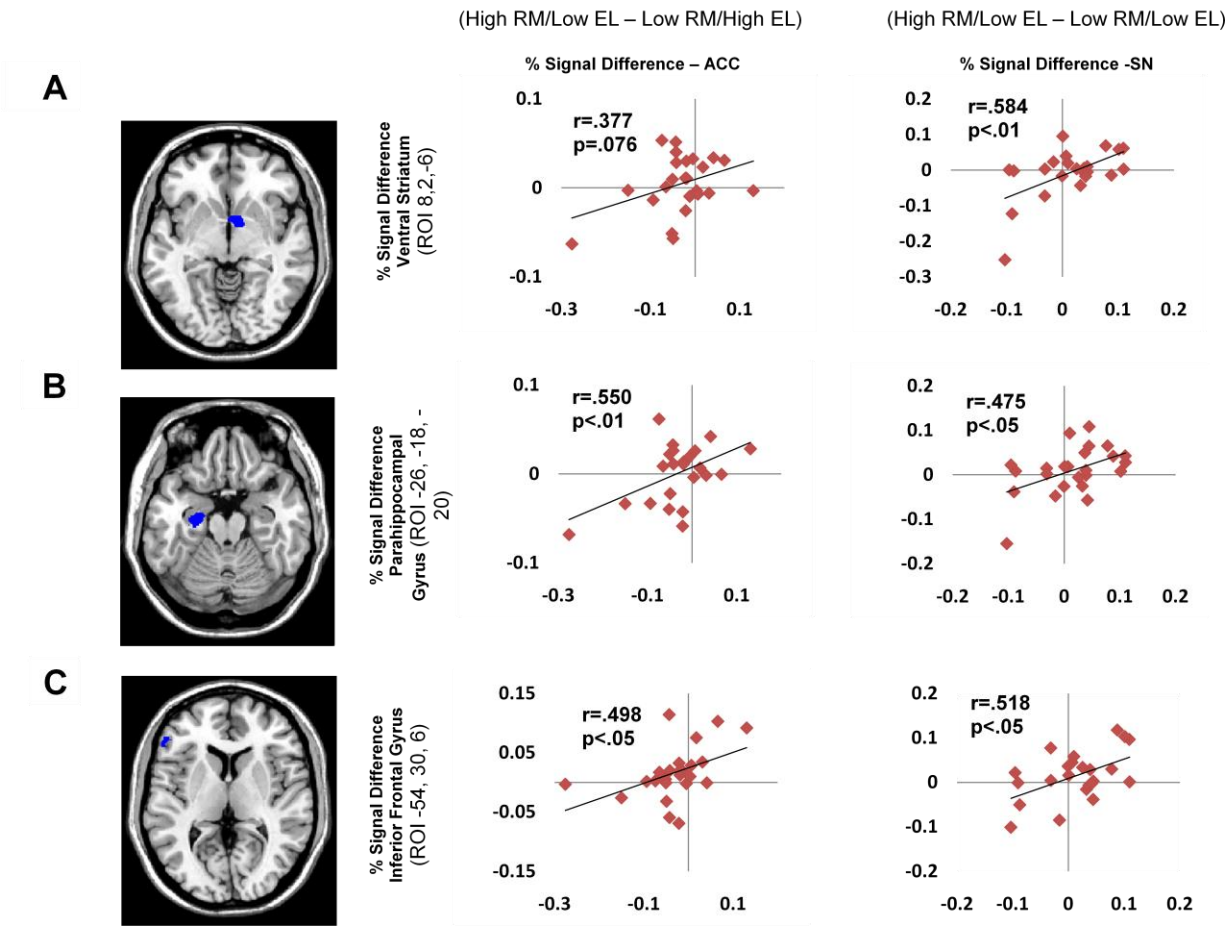


Figure S2. Across-subjects correlation of brain activation in ACC (middle column) and SN (right column) with other brain regions showing effects of reward magnitude.

Dopaminergic activation and training signals

In the main text, we tested two hypotheses about the origin of information related to reward magnitude in ACC and found no regions which could be the source of such information to ACC. We concluded that ACC therefore computes a representation of reward magnitude. What would the source of such signals to ACC and other brain areas be? One possibility is that dopaminergic (DA) midbrain signals (Schultz, 1998) may provide direct reward-related activation as well as training signals to ACC (Williams & Goldman-Rakic, 1998), as well as to other brain areas showing effects of reward magnitude. Models of ACC have suggested that activity in the substantia nigra (SN) acts as a training or inhibition signal to ACC (Holroyd & Coles, 2002; Brown & Braver, 2005; Holroyd, Yeung et al., 2005). According to this theory, unexpected withholding of rewards causes a transient depression in DA neuron activity, resulting in disinhibition of ACC. Other hypotheses suggest the opposite: that ACC activity inhibits SN, consequently depressing DA neuron activity (Frank, Woroch et al., 2005; Frank, D'Lauro et al., 2007). Additionally, dopaminergic signals might be expected to be involved in the calculation of expected value (Fiorillo, Tobler et al., 2003). The ICST involves monetary reinforcement with controlled error rates, and as such it is well-suited to investigate potential interactions between brain areas which encode reinforcement signals.

Localization of midbrain dopaminergic regions

Efforts to image midbrain areas and localize particular structures, especially the substantia nigra/ventral tegmental area (SN), which is a source of DA projections to cortex, entail a number of potential issues (D'Ardenne, McClure et al., 2008). Nevertheless, *a priori* assumptions about the localization of SN as well as patterns of interactions associated with reinforcement learning tasks can provide converging evidence that a particular region contains dopaminergic cells. To identify midbrain activity consistent with reward processing, we first defined an ROI corresponding to SN coordinates from the Talairach Demon database (Lancaster, Woldorff et al., 2000).

To further identify the SN, we note that heightened dopaminergic activity contributes to the likelihood of an individual to engage in financial risk-taking behaviors (Driver-Dunckley, Samanta et al., 2003). In the current study, reward likelihood varies inversely with error

likelihood, so the contrast of Low EL – High EL provides a measure of neural responses to reward likelihood. For task conditions in which a reward is likely (as in the Low EL condition), it is expected that phasic dopamine signals signaling a reward prediction should be greater than in task conditions in which a reward is not well-predicted. Gambling likelihood scores as measured by the DOSPERT (Weber, Blais et al., 2002) were regressed on activity in the SN ROI for the contrast (Low EL - High EL) in the low reward magnitude condition. If the area defined as SN contains neurons which show activity in response to reward, then a positive correlation between individual differences of financial risk-taking and activity in the SN region should exist. We found that as gambling likelihood increases across subjects, activity in an area of SN (peak correlation, MNI coordinates 8, -12, -8) related to reward likelihood likewise increases ($r=0.453$, $p<0.05$). One outlier was removed (Cook's distance 1.139). The correlation of the midbrain region with gambling likelihood scores provides converging evidence that the SN region contains cells sensitive to reward and risk, consistent with dopamine cell properties (Fiorillo, Tobler et al., 2003).

Interactions of regions showing reward magnitude effects, SN and ACC

Having isolated a region of the SN that is likely to provide dopamine signals, we are now in a position to assess whether the SN interacts with regions showing main effects of reward magnitude. The magnitude of the phasic dopamine signal at the onset of a reward predicting CS is known to be proportional to the level of the anticipated reward in monkeys (Tobler, Fiorillo et al., 2005), and additionally, tonic firing of DA neurons may be related to the probability (uncertainty) of receiving a predicted reward (Fiorillo, Tobler et al., 2003). While the phasic DA signal is thought to be integral to the computation of expected value (Schultz, 1998; Knutson, Taylor et al., 2005) it is uncertain what role tonic DA activity may have. To explore the possibility that midbrain region defined as SN may provide reward signals to other brain regions, we looked for correlations between the three regions showing main effects of reward magnitude and an ROI defined by the peak activity in SN found at 8, -12, -8 (figure S3). Since the phasic DA signal may be expected to be greatest for high probability, high value rewards, we performed an across-subjects correlation using the differences in reward magnitude (High RM – Low RM) in the low error likelihood condition for correct change trials between SN and each of the three ROIs showing reward magnitude effects above. Each of these areas showed a positive

correlation with activity in SN (figure S2). This suggests that midbrain dopamine signals may contribute to reward magnitude signals in the cortical regions, either as phasic dopamine bursts train the regions to respond to conditions of greater reward magnitude, or as phasic dopamine bursts directly activate the region

Interactions of ACC and SN

The hypothesized interaction between ACC and SN suggested by computational modeling (Brown & Braver, 2005) and neurophysiology (Ito, Stuphorn et al., 2003) suggests that transient depression of DA neurons below baseline firing rates should result in disinhibition of ACC, allowing ACC to learn representations of error likelihood. Characteristically, the DA signal in response to omitted, predicted rewards reaches a saturating non-linearity at the lower bound (i.e., no firing), suggesting that midbrain DA neurons asymmetrically encode reward and error (Bayer & Glimcher, 2005). However, for probabilistic reward (as in the present task), DA neurons have been found to show gradations in activity in response to omitted reward (Fiorillo, Tobler et al., 2003), with stronger suppression for more unexpected reward omissions. Therefore, differences in error processing in midbrain DA neurons should correlate with ACC activity. Specifically, depressions of baseline firing that are larger in magnitude or longer in duration should correlate negatively with higher ACC activity.

We therefore looked for a negative correlation between SN and ACC activity. We looked at the effect of errors vs. correct outcomes in the previously defined ROI in SN, using the change/high RM/low EL condition (contrast Change Error – Change/High RM/Low EL). Note that all errors which occurred following change signals were modeled as a single event in the GLM, regardless of reward magnitude or error likelihood conditions. This contrast was selected because it is the maximal difference between overall predicted expected value (i.e., the expected value is highest in the High RM/Low EL condition, which is expected to activate reward-related neurons in the midbrain) versus error trials, which are expected to result in transient depression of activity in those neurons. An across subjects correlation between the SN and ACC was performed for the contrast Go/Low RM/High EL – Go/Low RM/Low EL (Error likelihood effect). A significant correlation was found ($r=-0.452$, $p<0.05$; figure S2; one outlier was removed from the correlation [Cook's distance = 4.562]. This outlier was for the same subject as the outlier removed in the correlation between gambling likelihood scores and activity in SN.).

One possible interpretation of this finding is that as errors cause a greater depression of SN activity, there is a corresponding increase of ACC error likelihood effects. This finding is consistent with the predictions of the error likelihood computational model (Brown & Braver, 2005). If dopamine pauses train ACC representations of what events are happening when errors occur, then stronger dopamine pauses in error trials should in turn train stronger error likelihood signals in ACC, as seen in correct trials. Alternatively, ACC activity may inhibit SN activity. To investigate the direction of the causal interactions, we next turn to causal modeling.

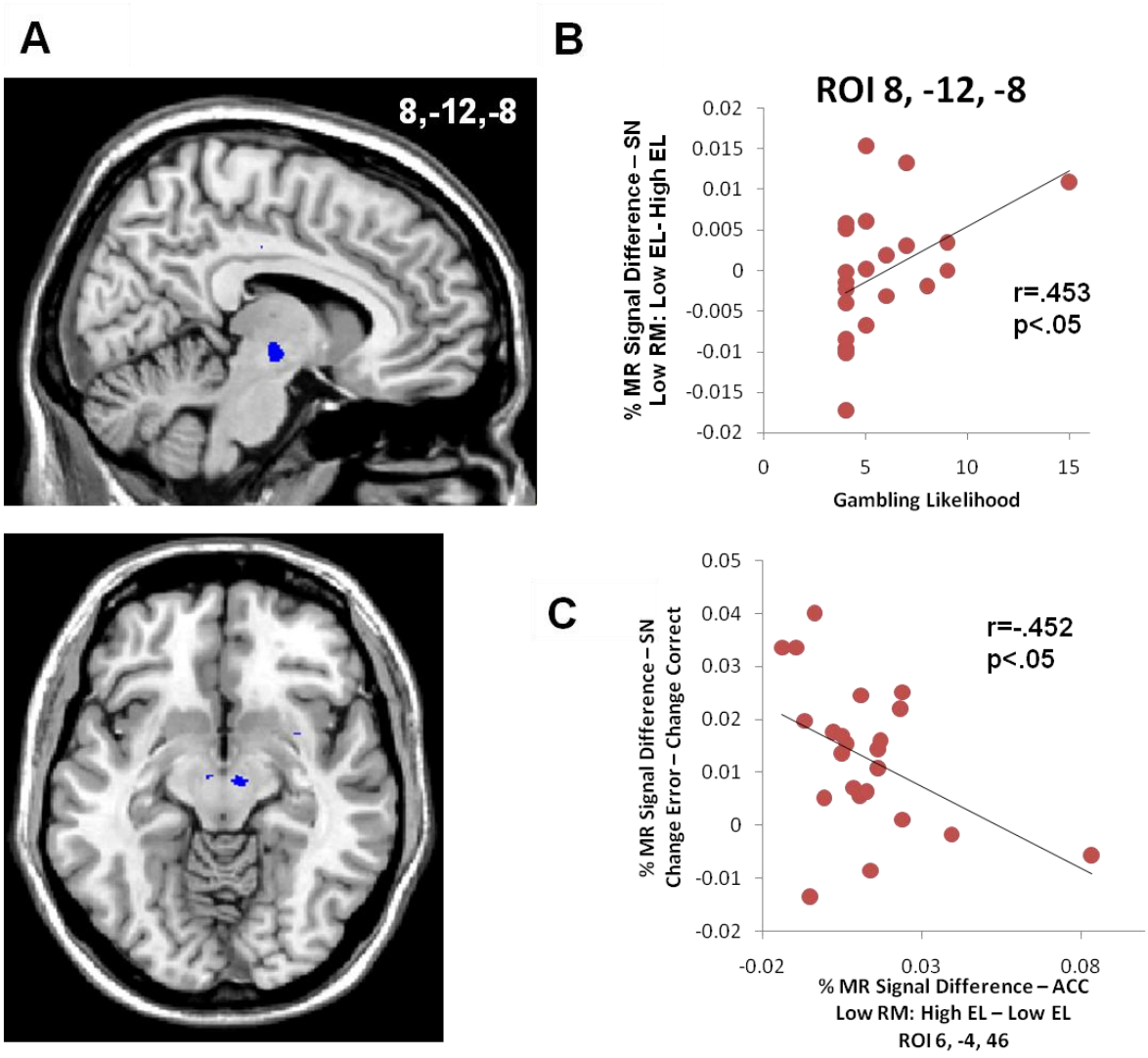


Figure S3. Interactions among ACC, SN, and risk-taking traits

Dynamic Causal Modeling (DCM)

For DCM analyses involving SN with additional areas (MOFC, PH, VStr, IFG; but not ACC), input to the DCM was again modeled as the onset of correct trials (see main text). Since SN was presumed to be involved only in the processing of reward-related information, only modulatory influences for levels of reward magnitude were estimated. Finally, for the correlation between ACC and SN, we were interested in testing exclusively the causal relationships only for error trials. To this end, input to the DCM was modeled as the onset of only error trials in the Change condition.

The results of the DCM analyses involving SN are summarized in table S1 along with DCM analyses involving ACC reported in the main text. A causal relationship was found from IFG to SN with a negative connection parameter, suggesting that IFG inhibits SN. A second causal relationship was found for the SN→VStr model, similar to that observed for DCM analysis between ACC and VStr. For none of these models was the value of the modulatory parameter estimate for reward magnitude significant. No evidence was found for a causal relationship between ACC and SN.

Supplementary Discussion

Overall, these results suggest that SN may contribute to reward-related activity in VStr, but the question of how other brain areas, including ACC, come to represent reward magnitude is not answered by the present analyses. One possible reason for the lack of evidence for interaction between midbrain and other structures in this study may be difficulties in imaging midbrain structures such as the SN/VTA that require specific targeting of the midbrain (D'Ardenne, McClure et al., 2008) combined with strong testable predictions. To identify putative dopaminergic regions of the midbrain, we combined previous reports of the spatial location of dopaminergic neurons (D'Ardenne, McClure et al., 2008) with observed interactions between these areas and other areas implicated in reinforcement learning. The expected location of the midbrain cells combined with the predicted and observed interactions with related regions together provided converging evidence that the midbrain regions were involved in reinforcement learning, as would be expected of dopamine cells. Specifically, the putative SN/VTA area

activity for high rewarding conditions correlates positively with individual differences on financial risk taking measures, as well as with other brain areas previously found to code expected value. DCM analyses suggest that SN may contribute to the prediction of reward observed in VStr (e.g., Elliot et al., 2000), while IFG, implicated in executive function and cognitive control (Bitan, Burman et al., 2006; Swick, Ashley et al., 2008), may implement control through modulation of midbrain structures underlying reward-seeking behavior.

Another key motivation for localizing reward-related midbrain regions is the hypothesized interaction of SN, a primary source in the midbrain of ascending dopaminergic projections, with ACC (Holroyd & Coles, 2002; Brown & Braver, 2005). Computational modeling suggests that ACC may learn representations of conditions which are likely to result in error commission through transient depression of DA activity below baseline, which in turn disinhibits cortical ACC neurons (Brown & Braver, 2005). As predicted by this hypothesis, we find activation of putative SN neurons in the midbrain that correlates negatively with activity in ACC. However, our attempt to assess the causal relationship between the two areas was inconclusive, and the possibility that ACC neurons inhibit SN activity via descending striatal projections has not been ruled out. We do note, however, that the results of our DCM analyses are consistent with observed neuroanatomy. In particular, VStr is known to receive projections from both SN and ACC (Eblen & Graybiel, 1995; Williams & Goldman-Rakic, 1998), and this connectivity is reflected in the finding of a causal influence of both SN and ACC on the VStr region in this study.

Previous studies found that error likelihood effects were reduced in participants who scored higher on measures of gambling likelihood and financial risk taking (Brown & Braver, 2007). Willingness to participate in financial gambles may reflect an underlying difference in how information about rewarding or aversive outcomes is processed in the brain, in that reward anticipation may be overweighted relative to risk prediction (Yechiam, Busemeyer et al., 2005). If dopaminergic error signals (i.e., transient pauses of dopamine cells) indeed train ACC representations of reward and error likelihood, then greater dopamine activity should be related to increased reward seeking, whereas reduced dopamine activity should be related to increased punishment sensitivity in the form of error likelihood and consequence magnitude prediction.

This is what we found in Figure S3, a finding that supports the hypothesized interactions between the SN/VTA and ACC.

				Average Parameter Estimates							
						Modulators				Contrast of Modulators	
Best Model	Alternative Models			Input Wt.	Conn. Wt	High RM	Low RM	High EL	Low EL	HRM-LRM t(1,22)	HEL-LEL t(1,22)
→ACC →VStr	**→ACC ↔VStr**	**ACC ←VStr←**	**ACC ↔VStr←**								
Avg. BF	69.92	60.19	727.94	0.114**	0.249**	-0.0833	-0.0835	-0.038	-0.129	-0.006	2.08*
→ACC→PH	**→ACC↔PH**	**ACC←PH←**	**ACC↔PH←**								
Avg. BF	78.23	9.27	390.47	0.11**	-0.051	-0.0725	-0.0434	-0.008	-0.108	-0.789	2.06
→ACC→IFG	**→ACC↔IFG**	**ACC←IFG←**	**ACC↔IFG←**								
Avg. BF	67.56	2.35	64.27	0.119**	-0.197*	-0.011	-0.006	0.039	-0.056	-0.102	1.36
→IFG→SN	**→IFG↔SN**	**IFG←SN←**	**IFG↔SN←**								
Avg. BF	10.88	9.09	129.39	-0.078**	-0.349**	0.162	0.102			1.482	
→PH→SN	**→PH↔SN**	**PH←SN←**	**PH↔SN←**								
Avg. BF	9.72	1.92	40.56	-0.057**	-0.360**	0.094	0.037			1.393	
→SN→VStr	**→SN↔VStr**	**SN←VStr ←**	**SN↔VStr ←**								
Avg. BF	6.51	4.63	23.03	0.071**	0.304**	-0.097	-0.117			0.51	
→MOFC→IFG	**→MOFC↔IFG**	**MOFC←IFG←**	**MOFC↔IFG←**								
Avg. BF	9.45	4.38	46.36	0.021	0.009	0.004	0.07			-0.09	
→MOFC→ACC	**→MOFC↔ACC**	**MOFC←ACC←**	**MOFC↔ACC←**								
Avg. BF	4.54	5.11	116.16	0.016	0.014	0.027	0.031			-0.13	
→MOFC→VStr	**→MOFC↔VStr**	**MOFC←VStr←**	**MOFC↔VStr←**								
Avg. BF	2.93	21.02	61.65	0.018	-0.007	0.0127	-0.012			0.798	
→MOFC→SN	**→MOFC↔SN**	**MOFC←SN←**	**MOFC↔SN←**								
Avg. BF	5.53	18.43	101.56	0.024	0.079	-0.044	-0.064			0.521	
→MOFC→PH	**→MOFC↔PH**	**MOFC←PH←**	**MOFC↔PH←**								
Avg. BF	7.70	6.14	54.41	0.011	0.041	0.031	0.027			0.151	
→ACC→SN	**→ACC↔SN**	**ACC←SN←**	**ACC↔SN←**								
Avg. BF	3.08	1.49	2.04	0.072**	0.313**						

Table S1. DCM analysis. The full results for all sets of DCM models examined. The best model in each set is given in the leftmost column, followed by group average Bayes factors for the comparisons against the alternative models, parameter estimates, and contrasts between modulatory influences (if applicable).

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