Supporting Information

Lawson et al. 10.1073/pnas.1323586111

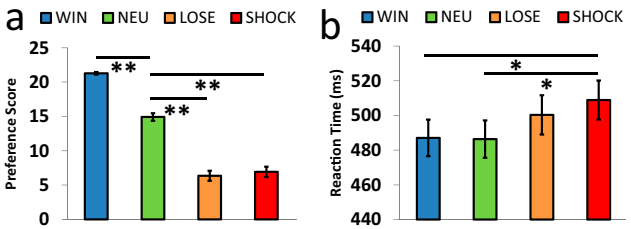

Fig. S1. Pilot data: indices of conditioning. Pilot data from a study conducted outside the scanner [$n = 20$; 10 female; mean age = 38.5 (SD = 8.03) y]. Subjects underwent a thresholding procedure as in the main study, rating each shock on a visual analog scale from 0 (not painful) to 10 (worst imaginable pain). Because subject movement was not a consideration in this pilot study, the average shock strength tolerated by subjects was higher: 20.3 (SEM = 4.76) mA. Subjects preferred to see loss and shock conditioned stimuli (CSs) least [significant effect of CS type: $F(3,57) = 105.56$, $P < 0.001$] (*A*), and subjects responded slowest in the flicker detection task when shock CSs were on screen [significant effect of CS type: $F(3,57) = 4.58$, $P = 0.006$] (*B*). Error bars represent SEM. *$P <$ 0.01; **$P < 0.001$.

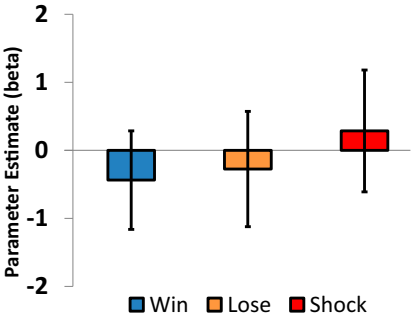

Fig. S2. Left habenula responses. Extracted blood oxygen level-dependent responses from the left habenula correspond to the dynamically changing values of win, loss, and shock CSs, averaged across subjects. The linear response profile is similar to the right habenula but is not statistically significant.

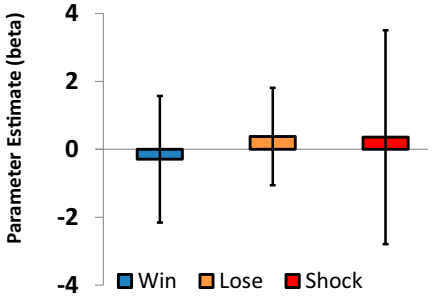

Fig. S3. Medial dorsal (MD) thalamus results. No significant blood oxygen level-dependent response to the value of win, loss, and shock CSs was detected in the combined left and right MD thalamus region of interest. Error bars represent SEM.

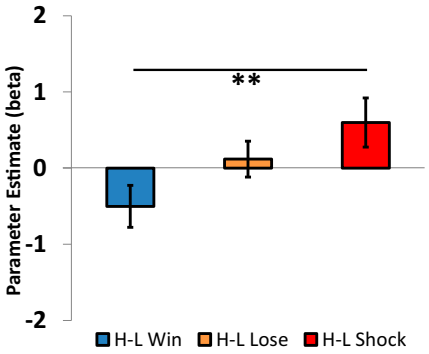

Fig. S4. Habenula response to high- vs. low-probability CS value. Extracted habenula blood oxygen level-dependent response (averaged across left and right) corresponds to the contrast of high- vs. low-probability (H-L) win, loss, and shock CSs, separate from trial-by-trial fluctuations in CS value. Error bars represent SEM.

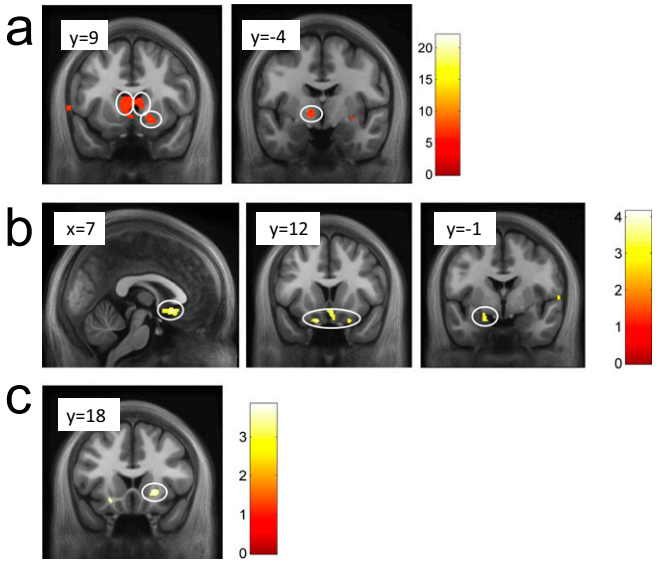

Fig. S5. Whole-brain connectivity analysis. (*A*) "Seed-based" connectivity (main effect of the physiological variable) over the entire functional MRI (fMRI) time series between the right habenula (seed region) and the right ventral striatum, bilateral medial wall of the caudate, and globus pallidus (images thresholded at $P < 0.05$, whole-brain family-wise error corrected at the voxel level). (*B*) Psychophysiological interaction analysis showing increased coupling between the right habenula and Brodmann area 25/posterior orbitofrontal cortex (*Left* and *Center*) and amygdala (*Right*) as a function of increasing shock CS value. Note that these regions were not included in our a priori regions of interest and are presented for information only. (*C*) Psychophysiological interaction analysis showing increased coupling between the right habenula and the right ventral striatum as a function of increasing win CS value (significant following small-volume correction in our striatal region of interest). Images in *B* and *C* are thresholded at $P < 0.005$ (uncorrected), with a cluster threshold (k) ≥10, and are overlaid on the average normalized anatomical image; color bars represent t values.

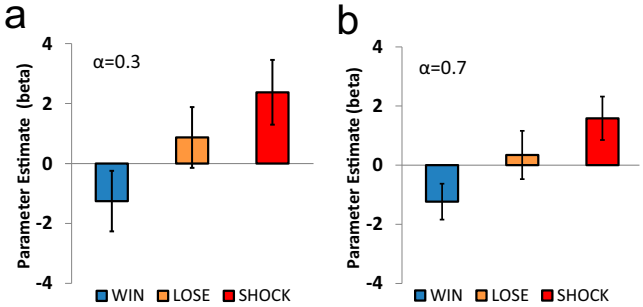

Fig. S6. Habenula ROI results at different learning rates. Similar results were obtained when using learning rates of (*A*) $\alpha = 0.3$ and (*B*) $\alpha = 0.7$ (original $\alpha = 0.5$). Error bars represent SEM.

Table S1. Whole-brain analysis: All activations for contrasts pertaining to the value of win conditioned stimuli (CSs), loss CSs, and shock CSs (exploratory $P < 0.005$, $k \geq 10$)

			MNI coordinates			
k	*t*	*Z*	*x*	*y*	*z*	Region
Shock value						
65	4.68	3.85	−68	−18	17	Parietal operculum
318	3.85	3.33	6	−21	2	Centromedian thalamic nucleus
	3.52	3.10	12	−17	5	Ventrolateral thalamic nucleus
	3.14	2.82	−3	−11	2	Anterior thalamus
68	3.60	3.16	−17	−6	2	Globus pallidus*
106	3.51	3.09	−42	−60	14	Posterior superior temporal sulcus
55	3.48	3.07	−44	−5	12	Frontal operculum
17	3.47	3.07	−63	5	11	Precentral gyrus
44	3.43	3.03	56	0	8	Precentral gyrus
37	3.31	2.95	−14	−27	−8	Medial geniculate nucleus
12	3.03	2.74	−3	−56	20	Posterior cingulate gurus
Lose value						
481	4.85	3.96	65	−8	6	Anterior temporal gyrus
	3.25	2.90	53	−12	−5	Anterior superior temporal cortex
467	4.19	3.55	−39	−65	17	Middle temporal gyrus
	3.28	2.92	−48	−51	12	Posterior superior temporal sulcus
625	4.11	3.50	38	−66	14	Middle temporal gyrus
	3.92	3.38	51	−63	14	Posterior superior temporal sulcus
	3.29	2.93	24	−74	18	Angular gyrus
64	3.69	3.22	30	63	−12	Inferior frontal gyrus
163	3.46	3.06	−63	−21	9	Superior temporal gyrus
	3.16	2.84	−68	−17	2	
38	3.27	2.92	−62	8	15	Inferior frontal gyrus
16	3.25	2.91	−60	−39	20	Posterior superior temporal gyrus
77	3.21	2.87	−38	−17	8	Posterior insula
	3.07	2.77	−32	−14	3	Insular claustrum
22	3.18	2.85	71	−23	2	Superior temporal gyrus
10	3.17	2.85	59	12	−11	Anterior superior temporal gyrus
17	3.14	2.82	33	−36	5	Caudate nucleus, tail
Win value						
668	4.31	3.63	−56	2	3	Lateral precentral gyrus
	4.06	3.47	−50	3	12	Precentral gyrus
228	4.25	3.59	38	−21	3	Posterior insula
	2.90	2.64	29	−14	8	Posterior putamen
886	3.92	3.38	12	48	3	Dorsal anterior cingulate
	3.47	3.06	−9	51	8	Dorsal anterior cingulate
	3.30	2.95	−11	59	−3	Rostrolateral prefrontal cortex
60	3.59	3.15	−45	39	−20	Lateral inferior frontal gyrus
41	3.35	2.98	26	−18	15	Putamen, posterior
86	3.21	2.87	−65	−47	0	Middle temporal gyrus
83	3.17	2.85	−38	29	−6	Orbital inferior frontal gyrus
	3.07	2.77	−42	35	−3	Inferior frontal gyrus
21	3.16	2.84	−50	−6	−8	Anterior superior temporal lobe
17	3.12	2.81	−20	8	14	Caudate/dorsal putamen
10	3.08	2.78	45	29	−14	Lateral orbitofrontal cortex
19	3.08	2.78	53	3	5	Lateral precentral gyrus
17	3.08	2.78	−56	−39	12	Posterior temporal gyrus
18	3.02	2.73	−66	−9	−8	Middle temporal gyrus
18	2.99	2.71	−54	−5	−15	Posterior superior temporal sulcus
11	2.93	2.67	−59	−24	2	Superior temporal sulcus

k, cluster threshold; MNI, Montreal Neurological Institute; *Z*, *Z* statistic.
*Globus pallidus region is discussed in the main text.

Table S2. Whole-brain analysis: Activations derived from the negative contrasts of win CS, loss CS, and shock CS values (exploratory $P < 0.005$, $k \geq 10$)

			MNI coordinates			
k	*t*	*Z*	x	*y*	*z*	Region
Negative shock value						
85	3.41	3.03	23	20	−23	Posterior orbitofrontal cortex
51	3.37	2.99	39	−3	−18	Claustrum
19	3.34	2.97	−23	15	−23	Posterior orbitofrontal cortex
40	3.24	2.90	−26	33	−20	Medial orbitofrontal gyrus
50	3.22	2.88	44	−75	6	Middle temporal gyrus
28	3.13	2.82	−26	9	−12	Piriform claustrum/ventral striatum
20	3.11	2.80	−21	−11	−15	Amygdala
14	3.09	2.78	29	9	−20	Piriform cortex
15	3.02	2.73	44	15	−20	Anterior superior temporal cortex
37	2.99	2.71	−39	36	−17	Orbitofrontal cortex
Negative lose value						
145	3.78	3.28	39	36	6	Lateral middle frontal gyrus
65	3.70	3.22	38	−90	5	Occipital gyrus
13	3.27	2.92	−8	−5	−8	Lateral hypothalamus
63	3.22	2.88	−5	18	−15	Medial posterior orbitofronal cortex
	3.08	2.78	−8	23	−21	
36	3.20	2.87	18	57	8	Superior frontal gyrus
12	2.97	2.69	−21	20	−14	Lateral posterior orbitofrontal cortex
Negative win value						
126	4.26	3.60	18	17	−17	Posterior orbitofrontal cortex
215	3.85	3.33	−12	−20	−12	Subthalamic nucleus/substantia nigra
	3.56	3.13	−6	−27	−11	Central tegmental tract ext. periacqueductal gray
	3.38	3	−14	−9	−14	Amygdala
19	3.26	2.91	14	−30	−3	Medial geniculate nucleus

ext., extending into.

Table S3. Psychophysiological interaction analysis: Main effect of connectivity with the habenula over all levels of the psychological factor ($P < 0.05$ family-wise error) and also as a function of increasing shock CS value and increasing win CS value (exploratory $P < 0.005$, $k \geq 10$)

			MNI coordinates			
k	*t*	*Z*	*x*	*y*	*z*	Region
Main effect connectivity with habenula						
6,994	21.52	Inf	5	−24	2	Habenula
	9.35	5.88	20	−21	−2	Ventral posterior thalamus*
	8.02	5.43	−2	−12	−2	Ventral anterior thalamus*
	7.43	5.2	−8	−8	−3	Globus pallidus*
	6.97	4.94	−11	5	6	Medial caudate*
	6.76	4.92	11	6	12	Medial caudate*
598	8.52	5.61	−56	−17	14	Parietal operculum
283	7.97	5.41	18	12	−8	Ventral striatum*
	6.49	4.8	27	2	−12	Amygdala*
	6.14	4.64	32	−5	−8	Claustrum
834	7.83	5.36	66	−24	−8	Middle temporal gyrus
	7.73	5.32	57	−26	−8	Middle temporal gyrus
	7	5.03	56	−12	11	Parietal operculum
1,470	7.35	5.17	47	−66	8	Posterior superior temporal sulcus
	7.02	5.03	60	−48	11	
	6.86	4.96	56	−42	14	
592	7.29	5.15	−12	−65	8	Primary visual cortex/BA17
139	7.21	5.11	−63	6	5	Inferior frontal gyrus
908	7.07	5.05	18	−60	9	Primary visual cortex/BA17
	6.98	5.02	6	−77	6	
	6.36	4.74	−2	−87	17	
142	6.84	4.95	−35	−33	17	Posterior insula
50	6.49	4.8	−56	−51	15	Posterior superior temporal sulcus
24	6.39	4.75	57	0	−15	Anterior superior temporal sulcus
53	6.27	4.7	−39	−81	15	Occipital/angular gurus
80	6.21	4.67	−48	−68	17	Angular gyrus
	6.17	4.65	−50	−74	9	
Connectivity with habenula modulated by shock CS value						
59	3.95	3.39	−15	15	−23	Posterior orbitofrontal cortex*
294	3.79	3.29	3	15	−12	Subcallosal anterior cingulate*
	3.58	3.14	6	17	−20	
218	3.75	3.26	56	−23	6	Superior temporal gyrus
	3.7	3.23	65	−32	14	Posterior superior temporal gyrus
22	3.4	3.01	−12	−12	−9	Globus pallidus internus
64	3.39	3	−18	2	−21	Amygdala*
26	3.38	3	−14	−51	5	Posterior cingulate gyrus
26	3.33	2.97	42	30	3	Medial frontal gyrus
24	3.27	2.92	39	−12	−14	Insular claustrum
65	3.19	2.86	−21	−44	11	Occipital/cingulate gyrus/ventricle
19	3.08	2.78	−56	29	−3	Inferior frontal gyrus
12	3.01	2.72	23	12	−21	Posterior orbitofrontal cortex
27	3.01	2.9	62	−8	3	Temporal gyrus
17	2.9	2.64	−71	−27	−2	Superior temporal gyrus
Connectivity with habenula modulated by win CS value						
172	3.54	3.11	23	18	−3	Ventral striatum*
	3.31	2.95	18	24	−9	Anterior putamen
22	3.34	2.97	−21	18	−12	Insular claustrum

BA17, Brodmann area 17; Inf, infinite.
*These regions are discussed in the main text.