Supplementary Materials

I. *Participant Recruitment and Characteristics*

A total of 18 PG and 25 HC participants, all European Americans, were included. Of the 18 PG subjects, 11 participants met criteria for Axis-I diagnoses (not active for >3 months if it was past) including one for past major depressive disorder and current cocaine dependence, one for current social phobia (public speaking), one for past cocaine abuse and current cannabis abuse, two for past alcohol abuse, one for current alcohol abuse, one for current alcohol dependence, two for past alcohol dependence and past cocaine dependence, one for past alcohol abuse and past cannabis abuse, one for past alcohol abuse and past cannabis dependence. The pattern of comorbidity is reflective of what we have seen in this clinical population. We evaluated the effects of the comorbidity on analysis of the primary PG diagnosis (details in Discussion). All HC subjects had no Axis-I disorders except possible ND (one ND in the HC group). All participants completed the Fagerstrom test for nicotine dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and reported no psychoactive drug use, except for nicotine or caffeine, for 72 hr before the imaging session. Urine testing was performed on the day of scanning to confirm abstinence and breathalyzer readings were performed to exclude individuals with recent alcohol consumption. Scores on the South Oaks Gambling Screen (SOGS), a valid and reliable problem-gambling screen (Lesieur & Blume, 1987), were used as a proxy indicator of problem-gambling severity. The protocol was approved by the Yale Human Investigation Committee. All subjects were recruited through advertisements and provided written informed consent.

II. Table S1. The demographics and clinical features of the study subjects in a 3-way 2 × 2 × 2 contingency table

	PG			**HC**		
***DBH* genotype**	**CC**	**T-carrier**		**CC**	**T-carrier**	
	Count	**Count**	**Subtotal**	**Count**	**Count**	**Subtotal**
Male	7	6	*13*	6	9	*15*
Female	2	3	*5*	5	5	*10*
Subtotal	*9*	*9*		*11*	*14*	

III. Table S2. Video viewing in random and counterbalanced order.

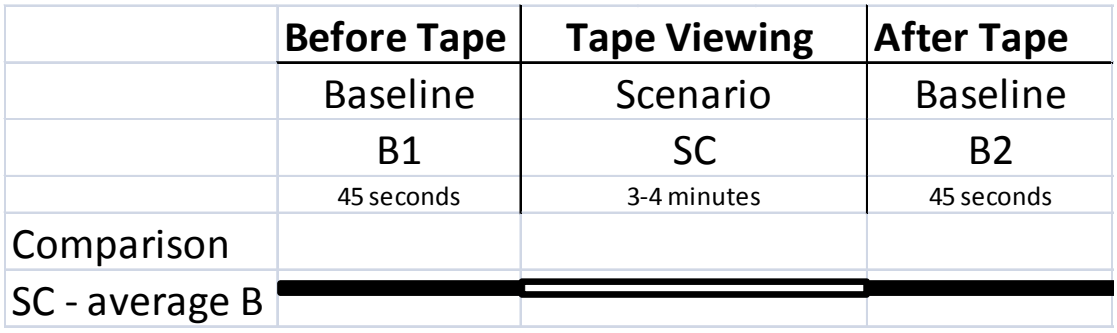
Report #	Video 1	Video 2	Video 3	Video 4	Video 5	Video 6
1	Cm1	Sf1	Gm1	Cf1	Gf1	Sm1
2	Cf2	Sm2	Gf2	Cm2	Gm2	Sf2
3	Gm1	Cf1	Sm1	Gf1	Sf1	Cm1
4	Gf2	Cm2	Sf2	Gm2	Sm2	Cf2
5	Sm1	Gf1	Cm1	Sf1	Cf1	Gm1
6	Sf2	Gm2	Cf2	Sm2	Cm2	Gf2

Note. There were two male actors and two female actresses for each of cocaine, gambling and sad scenarios. Cm1, cocaine male 1. Cm2, cocaine male 2. Cf1, cocaine female 1. Cf2, cocaine female 2. Gm1, gambling male 1. Gm2, gambling male 2. Gf1, gambling female 1. Gf2, gambling female 2. Sm1, sad male 1. Sm2, sad male 2. Sf1, sad female 1. Sf2, sad female 2.

IV. *Gambling, Sad and Cocaine Video Scenarios*

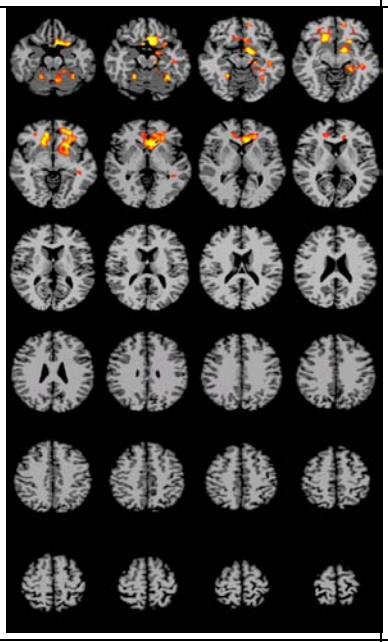
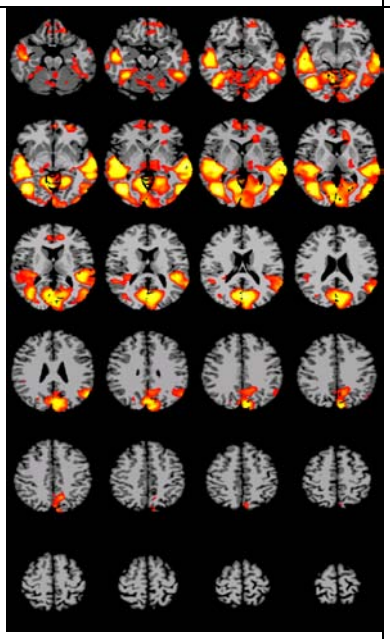
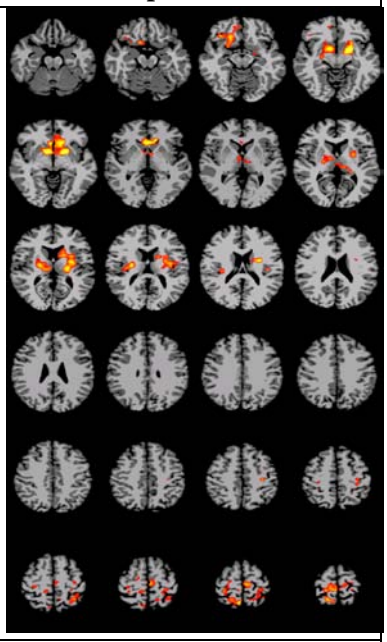
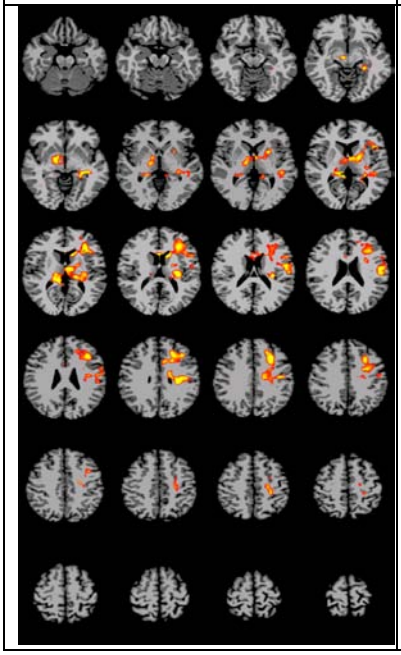
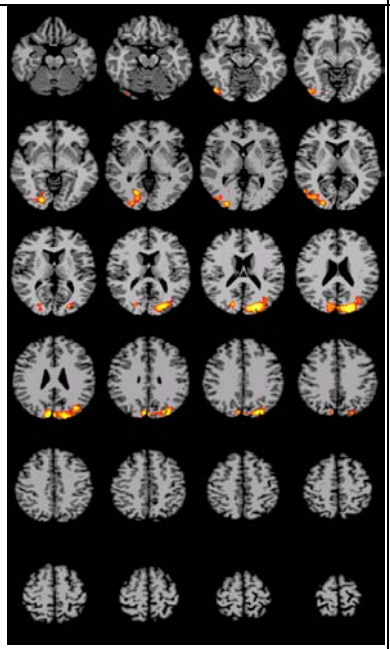
The sad scenarios describe parental divorce and a relative's death. The gambling scenarios describe recent emotional distress, the receipt of unexpected money and gambling at a casino. The cocaine scenarios describe recent emotional distress and frustration and the desire to get high and get a rush.

V. Figure S1. Epochs used in comparisons of brain activations in PG and HC subjects during viewing of sad, gambling-related and cocaine-related videos.



Note. SC indicates scenario of the three types of videos. "Average B" indicates the average of the baselines B1 and B2.

VI. Figure S2. Brain activation maps for the main effects of genotype and condition, and two-way interactions of group-by-condition and genotype-by-condition. Main effects of group and three-way interaction did not reveal findings surviving whole-brain correction. Images show the axial brain sections. The maps are thresholded at $p < 0.05$, with a family-wise-error correction. Right side of the brain is on the left. Maps span from Talaraich z = -14 mm (upper left) to z = 63 mm (lower right), at increments of 3–4 mm. The color bars indicating the strengths of findings (red/yellow), with yellow corresponding to more robust findings as compared to red.

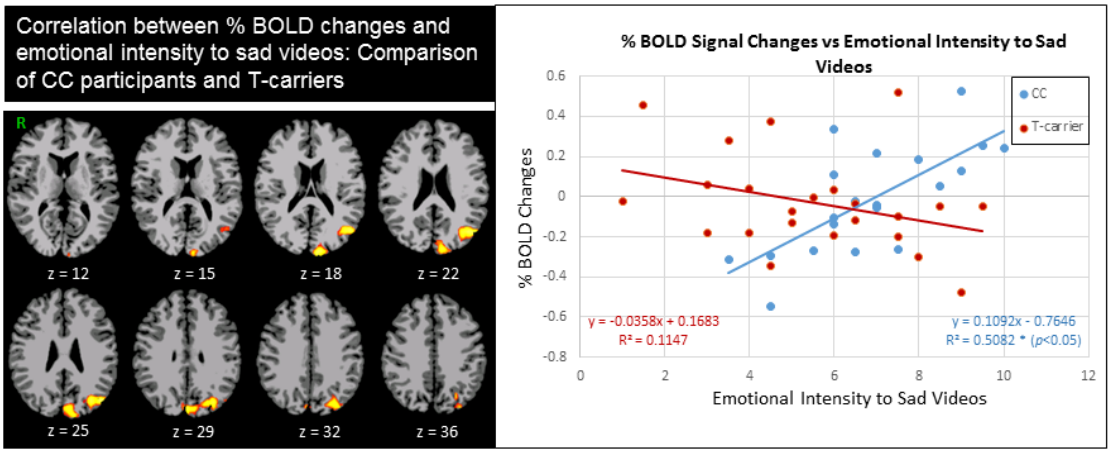
a. Main Effect of *DBH*	**b. Main Effect of Condition**	**c. Group x Condition**
		
d. *DBH* x Condition	**e. Group x *DBH***	
		**The Talaraich *z* values are as follows:** Row 1: -14,-11,-8,-4 Row 2: -1, 2, 5, 8 Row 3: 12, 15, 18, 22 Row 4: 25, 29, 32, 36 Row 5: 39, 42, 46, 49 Row 6: 52, 56, 59, 63

VII. *Subjective Responses to Gambling-, Sad- and Cocaine-Related Videos*

The subjective responses to the videos, involving ratings of emotional intensity, gambling urges and drug cravings, are summarized in Table S3. The gambling-related videos induced stronger gambling urges in PG compared to HC participants ($p < 0.00001$). Gambling urges between PG and HC also differed when viewing the sad and cocaine videos (sad videos, $p = 0.0017$; cocaine videos, $p = 0.0028$). Within the PG group, analysis of variance shows that gambling urges reported in response to gambling cues were stronger than those reported in response to cocaine or sad cues ($p = 1.64 \times 10^{-6}$), but drug urges and emotional intensity in response to all three cues showed no difference ($p = 0.075$ and $p = 0.356$). Pairwise comparisons within the PG group show that gambling urges in response to gambling cues are much stronger than cocaine and sad cues ($p = 5.6 \times 10^{-6}$, 5.69×10^{-6}, respectively), but no difference in gambling urges between cocaine and sad cues ($p = 0.95$). The counterpart pairwise comparisons within the HC group indicate no difference in gambling urges for any two cue types ($p = 0.058$–0.33). The findings may in part reflect a greater baseline gambling urge state that persists across conditions in the PG group; nonetheless, the greater gambling urge response to the gambling video versus the sad and cocaine videos in the PG group indicates a specificity of responsiveness as designed. The PG relative to HC participants also reported stronger emotional responses to the gambling videos ($p < 0.00001$). Drug cravings were relatively mild across videos and did not differ in the PG and HC groups (Table S3). The nature of the responses also differed to the gambling videos, with HC subjects typically reporting more varied and arguably negative responses (e.g., feeling annoyed, bored, mad, sad, but also sympathetic) and PG subjects typically reporting gambling urges and responses (e.g., feeling excited, a "rush," anxious, angry, excited, but also at times angry, sad, or guilty about the exhibited gambling behaviors). Responses to the sad videos were typically dysphoric across both groups. Responses to the cocaine videos were typically negative (e.g., feelings of anger, disgust, pity, madness, sadness, resentment) across both groups.

To further explore our hypothesis that T-carriers would show blunted/different responses to the sad videos as compared to CC participants, we examined the strengths of the correlations between emotional intensity ratings to the sad videos with brain activations to the sad videos in the CC participants as compared to those in the T-carriers (Figure S3). The strength of the correlation within the CC participants was statistically stronger (at a FWE-corrected $p < 0.05$ level) than that in the T-carriers in a cluster extending from the parietal cortex (including the inferior parietal lobule) to the inferior occipital gyrus (IOG). The IOG has been implicated in conveying information to the ventral prefrontal cortex in the processing of sadness, happiness, and anger (Dima, Stephan, Roiser, Friston, & Frangou, 2011). The parietal cortex has been implicated in the cognitive regulation of sadness (Belden, Luby, Pagliaccio, & Barch, 2014) and processing of facial affect (Belden et al., 2014).

Figure S3. Brain activation maps for the differences in the strengths of correlations in CC and T-carrier participants in the relationship between brain activation to the sad tapes and subjective responses to the sad tapes are shown (left). The maps are thresholded at $p < 0.05$, with a family-wise-error correction. The right side of the brain is on the left. Maps span from Talaraich $z = 12$ mm to $z = 36$ mm, as indicated. The color bars indicating the strengths of findings (red/yellow), with yellow corresponding to more robust findings as compared to red. A scatterplot showing differences in CC and T-carrier participants in the relationship between brain activation to the sad tapes and subjective responses to the sad tapes is shown (right).



VIII. *Further Analyses of Co-occurring Disorders in PG*

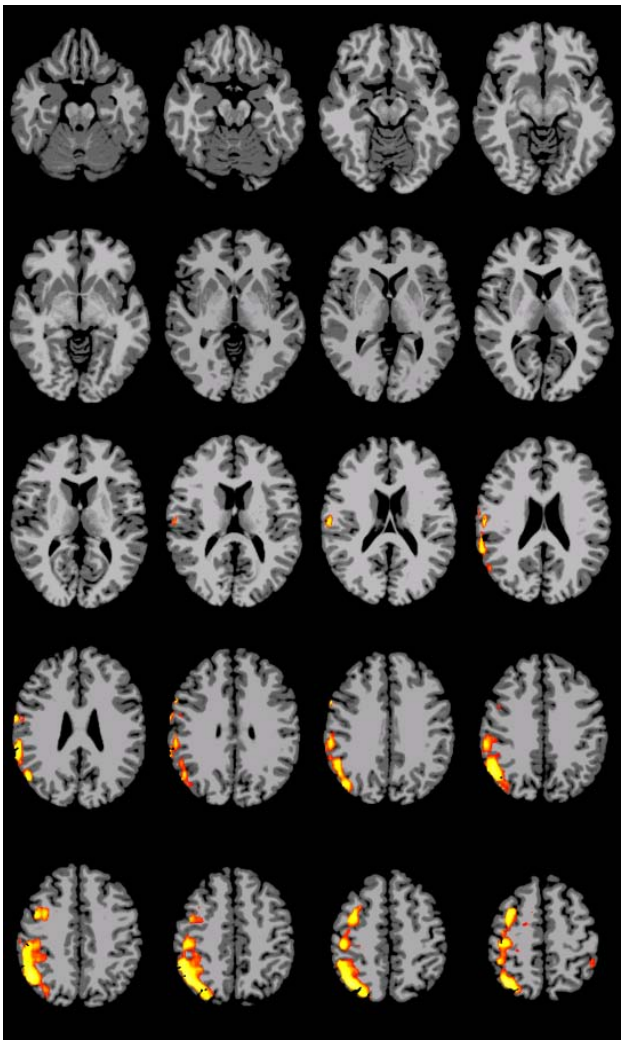
One imbalance is in co-occurring cocaine abuse/dependence. Three of the PG individuals met criteria for past cocaine dependence/abuse; when excluding these individuals from analyses, results were very similar.

Co-occurring alcohol dependence/abuse also differed within the PG group. Eight PG individuals met criteria for alcohol dependence/abuse. An analysis (covarying for age) investigating the neural responses between those with and without problematic alcohol use detected no differences both in the main effect of the problematic alcohol use and the interaction effect of the problematic alcohol use by the cue condition. On account of this analysis outcome, we conclude that the primary results reported for this study do not appear to be attributable to problematic alcohol use.

In order to examine possible influences of smoking, we explored brain activations in contrasts between smokers and nonsmokers within the PG group for the three scenarios (there was only one smoker in the HC group). Of the 18 PGs, 7 were smokers, 10 were nonsmokers, and 1 individual's smoking status was missing. No difference between smokers and nonsmokers was identified for the gambling and cocaine scenarios, but some differences emerged in the sad scenario. The proportion of females is balanced in the two groups and is 30% versus 29% in PG

smokers and nonsmokers, respectively. These effects did not appear to drive the observed results. However, PG smokers and nonsmokers showed some neural differences during the sad scenario in regions including the postcentralgyrus, supramarginalgyrus, angular gyrus, superior and inferior parietal gyri, and superior and middle occipital gyri (Figure S4).

IX. Figure S4. Brain activation map contrasting smokers and nonsmokers within the pathological gambling (PG) group during the sad scenario. Images show the axial brain sections. The maps are thresholded at $p < 0.05$, with a family-wise-error correction. Right side of the brain is on the left. Maps span from Talaraich $z = -14$ mm (upper left) to $z = 49$ mm (lower right), at increments of 3–4 mm. There were no significant influences of smoking status for the gambling and cocaine scenarios in the PG group. Red/yellow color indicates greater regional activation in smokers versus nonsmokers.



The Talaraich *z* values are as follows:

Row 1: -14,-11,-8,-4; Row 2: -1, 2, 5, 8 Row 3: 12, 15, 18, 22

Row 4: 25, 29, 32, 36 Row 5: 39, 42, 46, 49

X. Table S3. Replication analysis for the blood oxygen level dependent contrast in the PG versus HC groups for the center of mass of the two regions of interest (ROIs): ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS), in response to the gambling condition, focusing on the initial viewing of the videos (Epoch E0-baseline B1) in percent signal changes (Potenza et al., 2003). BioImageSuite was used for the ROI extraction. ROIs were chosen from the linear mixed effect results and then subclustered based on anatomical boundaries. While men with PG as compared to men without PG showed less VS activation (consistent with prior reports (Potenza, 2008)), the opposite pattern was observed in women.

vmPFC [sample size PG: HC]	PG-mean	PG-SD	HC-mean	HC-SD	*p* -value
all [18:25]	-0.076	0.305	-0.251	0.36	0.103
men [13: 15]	-0.009	0.302	-0.205	0.41	0.171
women [5:10]	0.062	0.264	-0.155	0.28	0.183
VS [sample size PG: HC]	**PG-mean**	**PG-SD**	**HC-mean**	**HC-SD**	***p* -value**
all [18:25]	-0.090	0.281	0.045	0.195	0.069
men [13: 15]	-0.117	0.280	0.095	0.217	*0.033**
women [5:10]	0.174	0.302	-0.077	0.134	*0.014**

References

Belden, A. C., Luby, J. L., Pagliaccio, D., & Barch, D. M. (2014). Neural activation associated with the cognitive emotion regulation of sadness in healthy children. Developmental Cognitive Neuroscience, *9*, 136–147. doi:10.1016/j.dcn.2014.02.003

Dima, D., Stephan, K. E., Roiser, J. P., Friston, K. J., & Frangou, S. (2011). Effective connectivity during processing of facial affect: Evidence for multiple parallel pathways. Journal of Neuroscience, *31*(40), 14378–14385. doi:10.1523/JNEUROSCI.2400-11.2011

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