Supplemental Materials

Pharmacological Treatment Similarities Between PG and Substance-Use Disorders

Opioid antagonists like naltrexone and nalmefene, initially found to be efficacious in the treatment of alcohol dependence, have more recently garnered empirical support in the treatment of PG (Grant, Kim, & Hartman, 2008; Grant, Odlaug, Potenza et al., 2010; Grant et al., 2006; Kim et al., 2001). Furthermore, individuals with PG who have a positive family history of alcoholism appear to respond better to these medications than do people without such a family history, suggesting that familial factors, likely biological ones, linking the disorders might be particularly relevant to treatment outcome to opioid antagonists (Grant, Kim, Hollander, & Potenza, 2008). Opioid antagonists have been hypothesized to operate through indirect modulation of the mesolimbic dopamine "reward" pathway, one widely implicated in substance addictions (Brewer & Potenza, 2008). A similar mechanism of altering ventral striatal (VS) function has been ascribed to the nutraceutical N-acetyl cysteine, an amino acid that may influence VS dopamine release through glutamatergic mechanisms (Kalivas & Volkow, 2005). Data suggest that like opioid antagonists, N-acetyl cysteine may have a role in the treatments of both PG and substance addictions like cocaine dependence (Grant, Kim, & Odlaug, 2007; LaRowe et al., 2006; LaRowe et al., 2007).

Material and Methods

Participants

Participants were 7 treatment-seeking individuals (2 females) with ages ranging from 41-56 years of age who met criteria for PG and nicotine dependence, were seeking help

for their gambling problems and participated in a double-blind, randomized, placebo-controlled trial of N-acetyl cysteine (see ClinicalTrials.gov [www.clinicaltrials.gov] with registry identifier NCT00967005). The inclusion of individuals with both PG and nicotine dependence was based on the frequent co-occurrence between the disorders, the greater problem gambling severity observed in this group (Bullock & Potenza, 2012; Grant, Kim, Odlaug, & Potenza, 2008; Grant & Potenza, 2005b; Potenza, 2007; Potenza et al., 2004), the need for improved treatments targeting co-occurring PG and nicotine dependence, and the potential utility of co-occurring disorders in targeting treatments for people with PG. The trial included twelve weeks of treatment with N-acetyl cysteine or placebo and six weeks of a cognitive-behavioral therapy (CBT) involving imaginal desensitization motivational interviewing (IDMI) as described elsewhere (Grant, Donahue, & Odlaug, 2011a, 2011b; Grant et al., 2009). IDMI therapy was initiated at week 7 of the trial. As the trial is ongoing, data blind to treatment condition is presented.

Participants were recruited via advertisements in the greater New Haven area. Supplemental Table 1 describes participant characteristics. PG was assessed by the Structured Clinical Interview for PG (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004) and co-occurring disorders were assessed via a Structured Clinical Interview for DSM-IV Disorders (SCID) (First, 1995). Six individuals were African-American, one was Caucasian and none had previously sought treatment for gambling problems. Two participants met criteria for past cannabis dependence, 4 participants met criteria for past cocaine dependence, 4 participants met criteria for past alcohol dependence, one participant had a history of polysubstance dependence and 2 participants had a history of major depression. Intelligence quotient (IQ) was assessed with the Shipley scale (Shipley,

Powell, & Harley, 1970). Severity of nicotine dependence was assessed via the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991). All participants were native English speakers with no head injuries. Toxicology tests at the time of scanning confirmed no other current illicit substance use.

This study was approved by the Yale Human Investigations Committee and all participants provided written informed consent. One participant dropped out of the treatment trial after their baseline session and another individual dropped out after week 6. The data from the latter participant at week 6 were carried over to week 12 (study end). A total of 6 individuals were therefore included in the correlational data. No additional subjects were scanned at the New Haven site of the trial, the only site that included scanning. Thus, the data should be considered preliminary in nature, demonstrating proof of concept.

CBT Treatment

The behavioral therapy employed was that described in detail in "Overcoming Impulse Control Problems: A Cognitive-Behavioral Therapy Program" (Grant et al., 2011a, 2011b). A therapist (CAF) was trained via viewing videotapes on delivering the manualized CBT. She next delivered the CBT in weekly individual sessions. The six sessions involved evaluating motivation to quit and introducing self-monitoring, financial planning and identifying triggers, identifying non-addictive pleasurable activities and preparing for trigger exposure, exposure therapy via guided imagery, identifying impulsive beliefs and employing alternate cognitive approaches, and relapse prevention. Getting one's gambling under control and stopping gambling were stated goals of the

CBT involving IDMI, although a subject need not be abstinent at study end to be considered a positive responder, as described below.

Measures

The Yale Brown Obsessive Compulsive Scale adapted for Pathological Gambling (PG-YBOCS)

The PG-YBOCS is a 10-item clinician-administered questionnaire developed to measure the severity and change of PG symptoms over the past 1-2 weeks. This scale has been validated, with good inter-rater reliability and internal consistency (Pallanti, DeCaria, Grant, Urpe, & Hollander, 2005). A significant reduction in PG-YBOCS scores has previously been reported in a PG population following NAC administration (Grant, Kim, & Odlaug, 2007). The PG-YBOCS was administered at baseline, Week 6 and Week 12.

fMRI Stroop Task

All participants performed an event-related fMRI Stroop color-word interference task and completed two practice runs prior to scanning (described in (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Potenza et al., 2003)). Word stimuli were presented on the screen for 1300 msec with a 350 msec intertrial interval with incongruent stimuli pseudo-randomly presented every 13-16 congruent stimuli. There were seven incongruent events in each run and participants completed a total of 6 runs with 105 stimuli (Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000). Behavioral Stroop performance was assessed out-of-scanner during five runs presented immediately

following scanning. A microphone recorded verbal responses as reaction times on each trial and errors on incongruent trials were manually recorded by research staff.

fMRI Acquisition and Analysis

Images were obtained on a Siemens TIM Trio 3T MRI system and analyzed largely as previously (DeVito et al., 2012), and as described below. Localizer images were acquired aligning the eighth slice parallel to the plane transecting the anterior and posterior commissures. Functional images were acquired with a T2*-weighed Blood Oxygen Level Dependent (BOLD) sequence with a TR of 1500ms, TE of 27, flip angle of 60°, 64 x 64 in-plane matrix, field of view of 220 x 220 and 25 4mm slices with 1mm skip. High-resolution 3D MPRAGE structural images were also acquired with a TR of 2530ms, TE of 3.34ms, flip angle of 7°, 256 x 256 in-plane matrix, and 176 1mm slices. Functional images were preprocessed using SPM5 (Welcome Functional Imaging Laboratory, London UK), normalized to the Montreal Neurological Institute template and smoothed with a 6mm kernel FWHM. First-level modeling was conducted using robust regression and motion parameters and high-pass filter parameters were included as additional regressors of no interest. A temporal high-pass filter of 128sec was used to remove low-frequency signals. Neuroelf analysis package (www.neuroelf.net) was used for second-level random effects analysis. Neuroelf is an analysis package for analyzing fMRI data that has been described and used in prior publications (Balodis et al., 2012; Balodis et al., in press; Brewer et al., 2011; DeVito et al., 2012; Kober et al., 2010; Montoya et al., 2012) and has advantages with respect to facilitating the use of advanced analytical approaches like robust regression and the rapid extraction by group and

condition of beta-weights contributing to observed fMRI findings. Correction for multiple comparisons was conducted using Monte-Carlo simulation (e.g., AlphaSim), using a combined voxel-wise and cluster thresholds to result in a family-wise-error (FWE) correction of $p<0.05$ as we have done previously (Balodis et al., 2012; Balodis et al., in press; DeVito et al., 2012; Montoya et al., 2012). An event-related design modeled the onsets of the incongruent and congruent stimuli of the Stroop task using the hemodynamic response function with a time derivative. T-tests were administered to assess for changes in Stroop-related activity using contrasts of incongruent versus congruent trials.

Results

PG-YBOCS scores at baseline (pre-treatment) and week 12 (end-of-treatment) are reported in supplementary Table 1.

Stroop Behavioral Performance

Reaction times recorded from out-of-scanner recordings of Stroop performance demonstrated a significant difference between congruent and incongruent stimuli (t=-10.66, p<.001), whereby the reaction time to incongruent stimuli [M=835.84(SD=39.98)] was significantly longer than the reaction time to congruent stimuli [M=609.91(SD=55.41)]. There was an overall error rate of 4.2% on incongruent trials.

fMRI Results

fMRI Stroop Effect

The main effect of Stroop trials is depicted in Supplementary Figure 1. The contrast of incongruent versus congruent trials produced a large significant cluster in the left

superior temporal gyrus (11957 voxels); subclusters extended to a variety of areas including the bilateral anterior cingulate, inferior frontal gyrus and medial prefrontal cortex and subcortical areas including the thalamus and the striatum.

Discussion

In the sample of subjects seeking treatment and performing pre-treatment Stroop tests, we observed largely anticipated patterns of behavioral responses and neural activations, similar to findings from our prior studies including those involving individuals with substance addictions or PG (Brewer et al., 2008; DeVito et al., 2012; Potenza et al., 2003). Specifically, reaction times to incongruent stimuli were longer than those to congruent ones, and brain activations observed involved regions previously implicated in Stroop performance and other cognitive control tasks including regions of dorsolateral prefrontal cortex, anterior cingulate, insula, thalamus, striatum and parietal and occipital cortices. These findings suggest that individuals were performing the Stroop task as instructed.

Our hypothesis (hypothesis 1) that baseline problem-gambling severity as assessed by PG-YBOCS scores would correlate inversely with activations in the vmPFC and VS during Stroop performance was partially supported. Specifically, correlations with VS activation were more evident than were those with vmPFC, although some activation in more dorsal vmPFC (involving the ventral anterior cingulate) correlated with problem-gambling severity. Within the anterior cingulate, there was a more pronounced correlation between problem-gambling severity and activity in the dorsal anterior cingulate; this region has been implicated not only in Stroop performance but also in

gambling-related activities such as loss-chasing (Campbell-Meiklejohn et al., 2008), responses to near-misses (Clark et al., 2010), and the relationship between personal control and responses to near-misses (Campbell-Meiklejohn et al., 2008; Clark et al., 2010; Potenza, Leung, et al., 2003). In the VS, correlations were observed bilaterally and involved the nucleus accumbens, a structure frequently implicated in studies of both substance and non-substance addictions including studies of PG. In particular, individuals with PG have shown relatively diminished VS during reward processing, simulated gambling and viewing of gambling-related stimuli (Balodis et al., 2012; Potenza, 2008; Reuter et al., 2005). Therefore, in conjunction with findings linking problem-gambling severity to vmPFC and VS activation during simulated gambling to problem-gambling severity (Reuter et al., 2005), these findings suggest that VS activation in particular across a broad range of processes might be closely linked to problem-gambling severity.

Our hypothesis (hypothesis 2) that pre-treatment fMRI Stroop measures in the VS and vmPFC would predict or associate with reductions in problem-gambling severity was partially supported. These results resonate with findings in cocaine dependence in which pre-treatment fMRI Stroop activations in the striatum and vmPFC correlated positively with better outcome as assessed by drug abstinence measures (Brewer et al., 2008). Specifically, changes in problem-gambling severity correlated positively with pre-treatment vmPFC and VS activations such that diminished activation at treatment onset correlated with more robust changes in PG-YBOCS scores. That is, less vmFPC and VS activation at treatment onset was associated with more robust clinical improvement, thus contrary to the direction observed in cocaine dependence (Brewer et al., 2008). Several possibilities exist. First, differences in outcome measures exist for the two studies, with

urine toxicology results used in the cocaine dependence study and change in PG-YBOCS scores used in the pilot PG study. It is possible that the pilot findings reflect the greater room for clinical improvement in the more severely affected individuals with PG. Second, differences between cocaine-dependent and PG subjects in neural activations have been reported for cravings/urges (Leeman & Potenza, 2012; Potenza, 2008) and during the processing of monetary rewards (Balodis et al., 2012; Jia et al., 2011). Thus, some of the between-group differences showing seemingly different or opposite patterns in contrasts of PG versus comparison subjects and cocaine-dependent versus comparison subjects may relate differently to treatment outcomes in PG and cocaine dependence, respectively.

In the current pilot study, the region of vmPFC identified as correlating with treatment outcome was more ventral than the region of anterior cingulate involving dorsal aspects of vmPFC associating with baseline problem-gambling severity. The identification of VS activation correlating with baseline problem-gambling severity and changes in problem-gambling severity suggests that the change relating to baseline VS activation may be in part accounted for by baseline severity. In contrast, the absence of a correlation between baseline PG-YBOCS scores and activity in the vmPFC region associating with treatment outcome suggests treatment improvement in this area is less closely linked to baseline severity scores. These findings could suggest a differential relationship between the relationships between VS and vmPFC activations whereby the changes in problem-gambling severity related to VS activation are accounted for baseline problem-gambling severity whereas those related to vmPFC activation are less so or not.

However, there are limitations to be considered with respect to these interpretations (as described in the main text of the manuscript).

In addition to limitations explicated in the main text of the manuscript, it is also possible that N-acetyl cysteine might contribute to treatment outcome. Such a possibility would seem consistent with N-acetyl cysteine's ability to modulate through glutamatergic mechanisms function within the VS and thus influence activity within a broader set of brain regions underlying cognitive control (Worhunsky et al., in press) and relate to its positive influences on PG treatment outcome (Grant et al., 2007). Additionally, although all subjects were provided with the opportunity to smoke approximately 60 minutes prior to fMRI in order to avoid acute influences of tobacco intoxication of withdrawal, severity of smoking may influence the findings. Given the preliminary nature and the small sample, these possibilities should be examined in larger samples.

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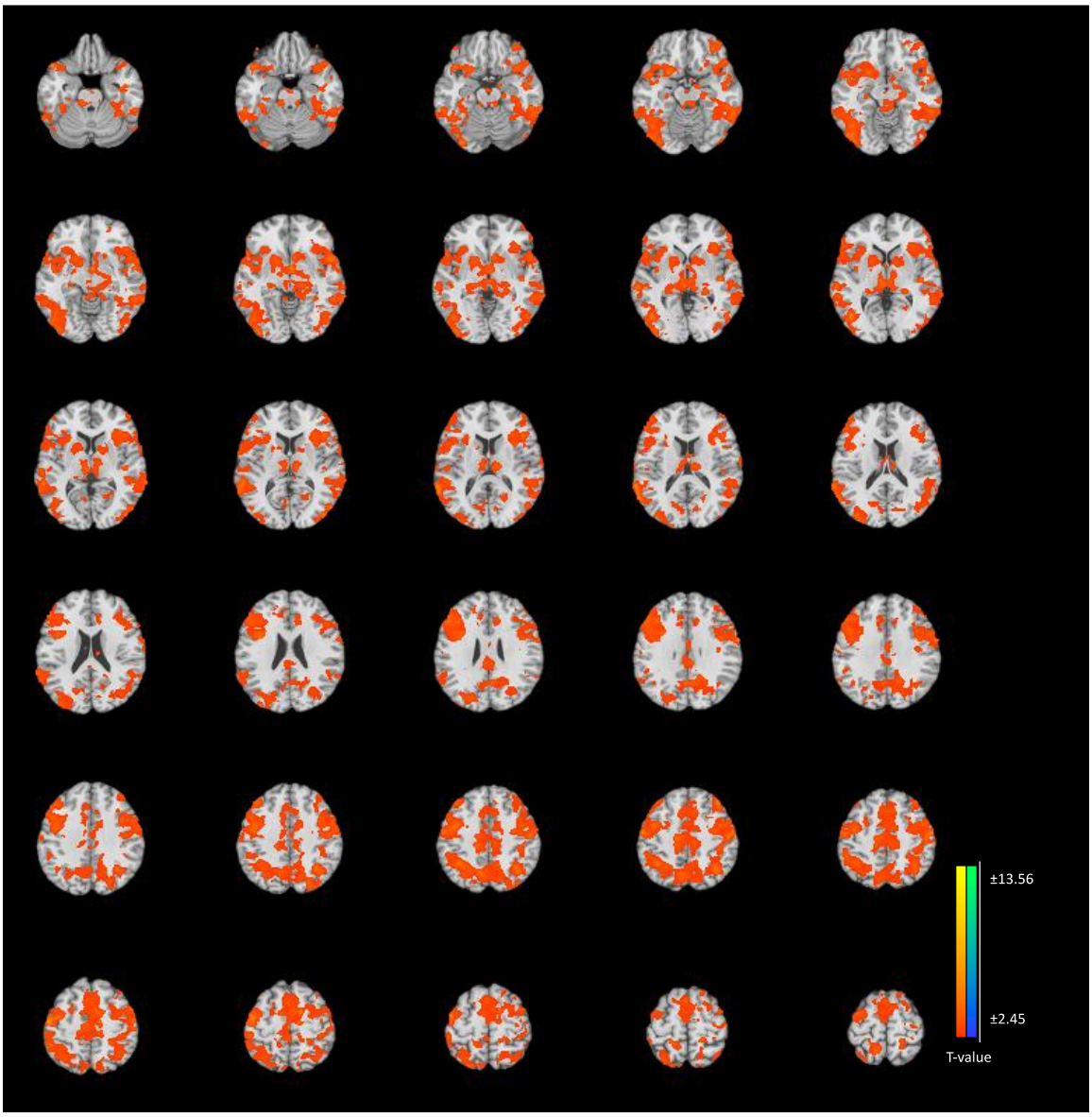
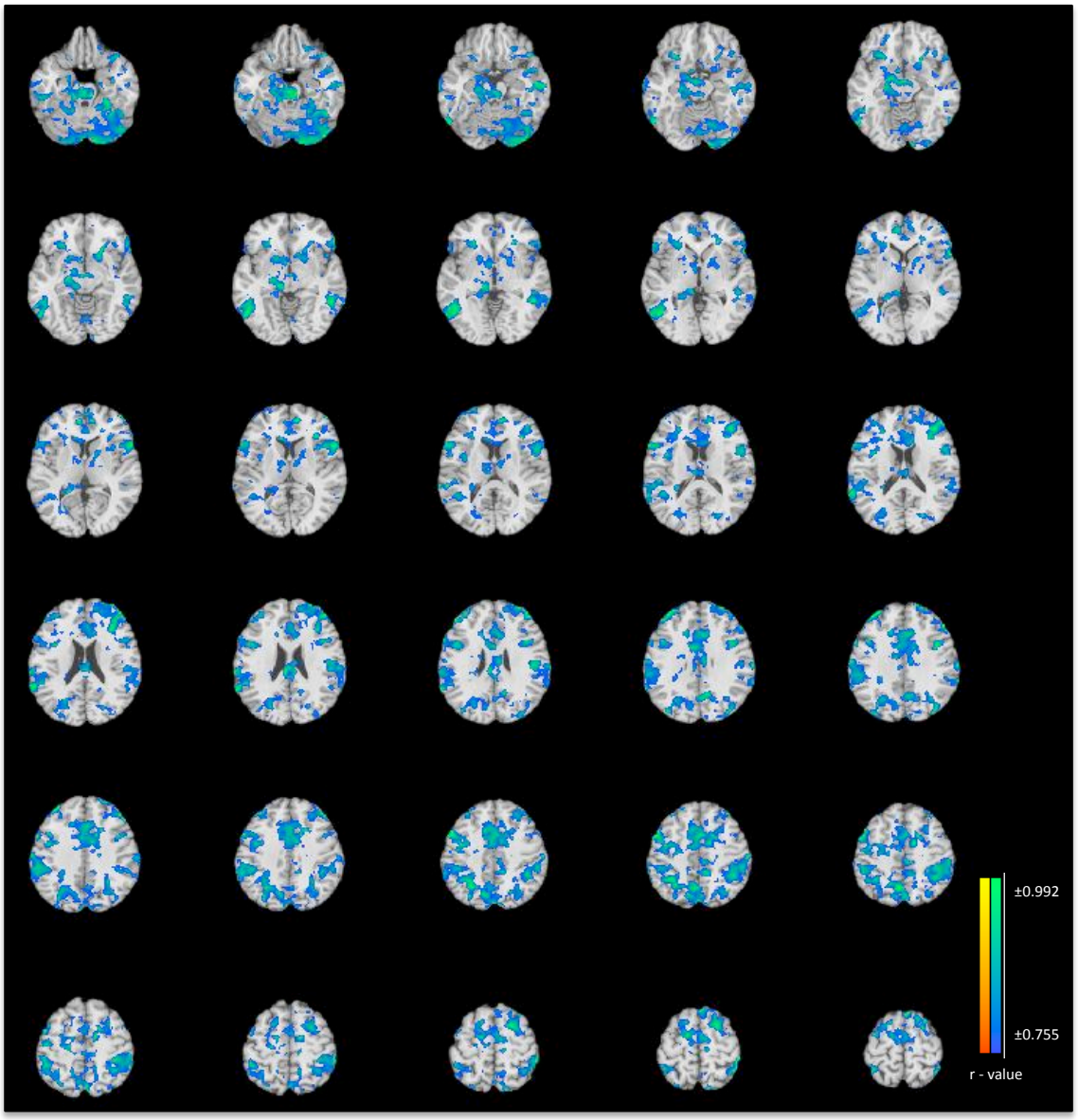
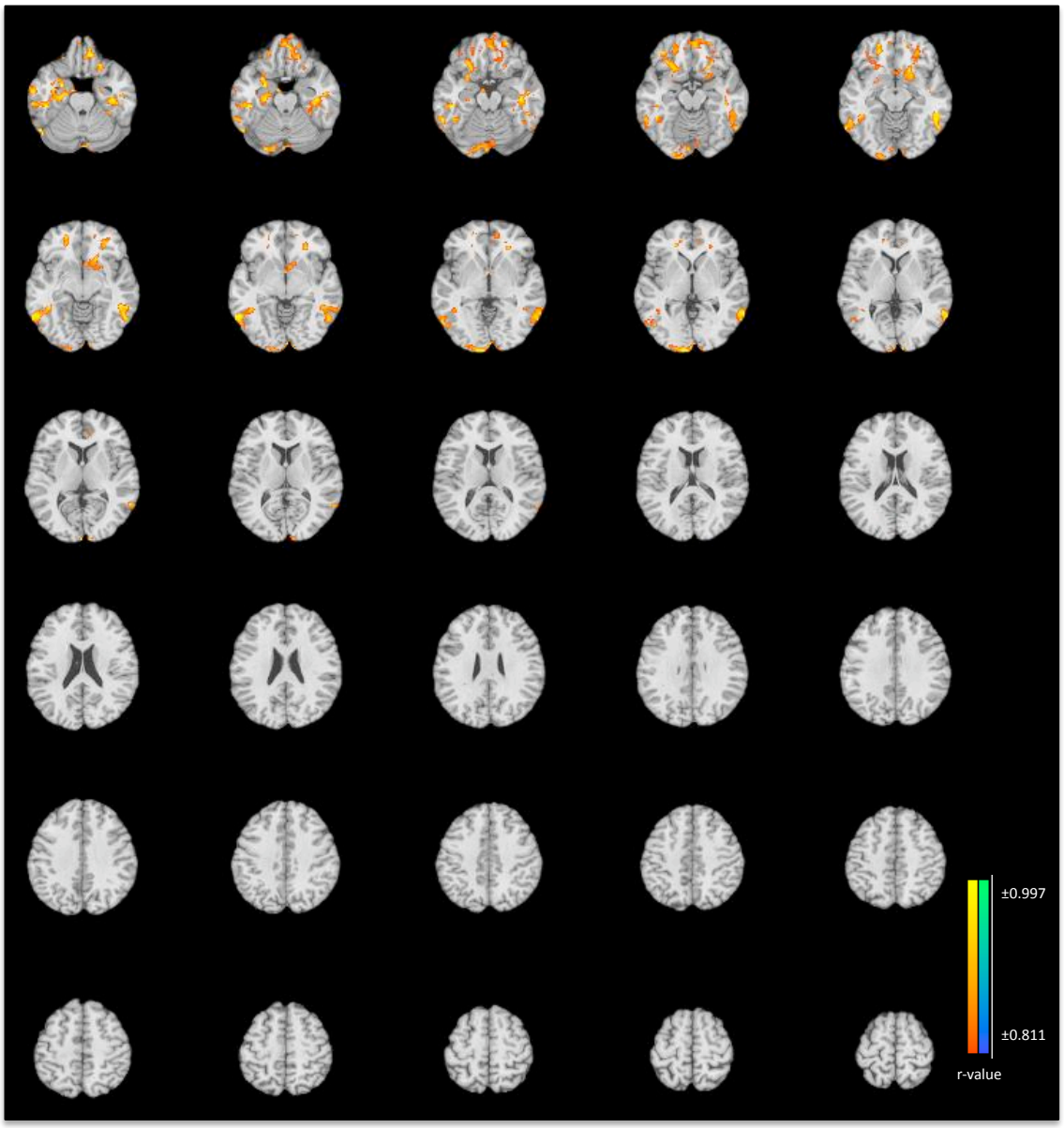


Supplemental Figure 1. Main Effect of Stroop Task Performance. Change in fMRI BOLD signal related to the Stroop-effect, contrasting incongruent trials with congruent trials in seven PG participants. The contrast map is thresholded at an uncorrected level of $p < 0.05$ two-tailed and FWE-corrected at $p < 0.05$ with a cluster threshold of 90. Red/orange color indicates areas of relative greater activity during the incongruent condition and blue/green indicates areas of relative lesser activity during the incongruent condition (none identified). The right side of the brain is on the right. Maps begin at MNI levels z=-25 and increase in steps of 3 to z=62. BOLD = blood oxygenation level-dependent; FWE = family-wise error; MNI = Montreal Neurological Institute; PG = Pathological Gambling



Supplemental Figure 2. Correlation between Stroop task performance and PG-YBOCS scores at baseline. Axial views of regional brain activation during Stroop task performance (contrasting incongruent trials with congruent trials) that correlated with scores on the PG-YBOCS in seven PG participants. The contrast map is thresholded at an uncorrected level of $p < 0.05$ two-tailed and FWE-corrected at $p < 0.05$ with a cluster threshold of 90. Blue/green color indicates areas of negative correlations between PG-YBOCS scores and percent BOLD signal changes in the incongruent versus congruent contrast, and orange/yellow color indicates areas of positive correlations (none identified). The right side of the brain is on the right. Maps begin at MNI level z=-25 and increase in steps of 3 to z=62. BOLD = blood oxygenation level-dependent; FWE = family-wise error; MNI = Montreal Neurological Institute; PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for Pathological Gambling



Supplemental Figure 3. Correlation between Stroop task performance and change in PG-YBOCS scores. Axial views of regional brain activations during Stroop task performance (contrasting incongruent trials with congruent trials) that correlated with changes in scores on the PG-YBOCS (week-12 score minus baseline score) in six PG participants. The contrast map is thresholded at an uncorrected level of $p < 0.05$ two-tailed and FWE-corrected at $p < 0.05$ with a cluster threshold of 90. Orange/yellow color indicates areas of positive correlations between changes in PG-YBOCS scores and pre-treatment percent BOLD signal changes in the incongruent versus congruent contrast, and blue/green color indicates areas of negative correlations (none identified). The right side of the brain is on the right. Maps begin at MNI level z=-25 and increase in steps of 3 to z=62. BOLD = blood oxygenation level-dependent; FWE = family-wise error; MNI = Montreal

Neurological Institute; PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for Pathological Gambling

Supplementary Table 1. Characteristics of treatment-seeking participants.

	Participants
n	7
Male/Female	5/2
Mean Age (SD)	48.4 (6.0)
Mean Years of Education (SD)	13.14 (1.5)
Mean Estimated IQ (SD)	93.14 (8.7)
Median Personal Income Reported	$15,000-24,999
Median Household Income Reported	$25,000-34,999
Mean Number of cigarettes/day (SD)	15.0 (5.0)
Mean Fagerstrom Nicotine Dependence Scale Score (SD)	5.29 (2.43)
Mean Baseline PG-YBOCS Total Score (SD)	24.14 (9.14)
Mean Baseline PG-YBOCS Urge Score (SD)	10.86 (5.18)
Mean Week-12 PG-YBOCS Total Score (SD)	7.60 (7.5)
Mean Week-12 PG-YBOCS Urge Score (SD)	5.00 (3.7)

Supplementary Table 2. Stroop main effect correlations with PG-YBOCS scores at baseline

Stroop Main Effect Contrast	Structure	BA	Left/ Right	MNI Coordinates x	y	z	k	Peak R-value
Incongruent> Congruent	Precuneus/Middle Frontal Gyrus/Inferior Temporal Gyrus/Middle Frontal Gyrus/Striatum/Cingulate/Middle Temporal Gyrus/Midbrain Substantia Nigra/Parahippocampal Gyrus/Amygdala/Medial Frontal Gyrus/Angular Gyrus/ Posterior Cingulate/Precuneus/Precentral Gyrus/Inferior Occipital Gyrus/ Superior Occipital Gyrus/Inferior Parietal Lobule/Thalamus/Declive/Culmen/Fusiform/Precuneus/Insula/Postcentral Gyrus/	7	L	-6	-60	48	10168	-0.995
	Inferior Temporal Gyrus/Fusiform/Middle Temporal Gyrus	20	R	63	-18	-36	186	-0.979
	Superior Parietal Lobule/Insula/Supramarginal Gyrus/Inferior Parietal Lobule/Superior Temporal Gyrus/	7	R	27	-48	72	803	-0.978
	Inferior Temporal Gyrus/Parahippocampal Gyrus/	20	L	-60	-24	-30	202	-0.954
	Middle Temporal Gyrus	20	R	36	-9	-27	116	-0.946

BA = Brodman's Area; MNI = Montreal Neurological Institute; k = cluster size in voxels; r = Pearson's correlation coefficient

Maps were thresholded at a voxel level of $p<0.05$ (two-tailed) using a conjoint family-wise-error (FWE) correction of $p<0.05$ to adjust for whole-brain comparison.

Individual clusters identified as surviving whole-brain correction are tabulated, with individual structures contained within each cluster indicated.

Supplementary Table 3. Stroop main effect correlations with changes in PG-YBOCS scores

Stroop Main Effect Contrast	Structure	BA	Left/ Right	MNI Coordinates x	y	z	k	Peak R-value
Incongruent> Congruent	Fusiform Gyrus	37	R	51	-42	-21	178	0.999
	Hippocampus/Parahippocampal Gyrus/Superior Temporal Gyrus/Middle Frontal Gyrus/Fusiform Gyrus/Inferior Frontal Gyrus/Amygdala	36	L	-39	-24	-30	596	0.997
	Fusiform Gyrus/Middle Temporal Gyrus/Inferior Temporal Gyrus/Parahippocampal Gyrus/Hippocampus	20	R	45	-27	-27	256	0.992
	Orbital Gyrus/Rectal Gyrus/Ventral Striatum/Inferior Frontal Gyrus/Superior Frontal Gyrus/Caudate/Anterior Cingulate Gyrus	11	R	3	48	-21	345	0.990
	Middle Temporal Gyrus	37	L	-60	-57	-9	216	0.987
	Cuneus/Inferior Occipital Gyrus/Cerebellum/Lingual Gyrus	18	L	-6	-105	-3	229	0.981

BA = Brodman's Area; MNI = Montreal Neurological Institute; k = cluster size in voxels; r = Pearson's correlation coefficient

Maps were thresholded at a voxel level of $p<0.05$ (two-tailed) using a conjoint family-wise-error (FWE) correction of $p<0.05$ to adjust for whole-brain comparison.

Individual clusters identified as surviving whole-brain correction are tabulated, with individual structures contained within each cluster indicated.