

Title:
Cue-Induced Brain Activity in Pathological Gamblers¹

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Abstract:

Background: Previous studies using functional Magnetic Resonance Imaging (fMRI) have identified differential brain activity in healthy subjects performing gambling tasks and pathological gambling (PG) subjects with motivational and emotional predecessors for gambling and during tasks requiring response inhibition. The goal of the present study was to determine if PG subjects exhibit differential brain activity when exposed to visual gambling cues. **Methods:** 10 male DSM-IV-TR PG subjects and 10 matched healthy controls underwent fMRI during visual presentations of gambling-related video alternating with video of nature scenes. **Results:** PG subjects and controls exhibited overlap in areas of brain activity in response to the visual gambling cues; however, compared to control subjects, PG subjects exhibited significantly greater activity in the right dorsolateral prefrontal cortex (DLPFC), including the inferior and medial frontal gyri, the right parahippocampal gyrus, and left occipital cortex, including the fusiform gyrus. PG subjects also reported a significant increase in mean craving for gambling after the study. Post-hoc analyses revealed a dissociation in visual processing stream (dorsal vs. ventral) activation by subject group and cue type. **Conclusions:** These findings may represent a component of cue-induced craving for gambling or conditioned behavior that could underlie pathological gambling.

Introduction:

Pathological gambling (PG) is characterized by persistent and recurrent maladaptive gambling behavior (American Psychiatric Association 2003). It is common with a lifetime prevalence of 1-2% (Shaffer & Hall 2001) and is associated with significant morbidity (Crockford and el-Guebaly 1998; Potenza et al 2001). Up to one half of PG subjects report that direct presentation of gambling stimuli is a trigger to gamble (Grant and Kim 2001), with males reporting a greater likelihood to gamble secondary to gambling sensory stimuli (billboards, advertisements, sights, sounds, hearing people talk about gambling) and women more often reporting emotional cues (Grant and Kim 2002). As identifying cues/triggers for gambling is reported as an essential aspect of relapse prevention in the treatment of PG subjects (Ladouceur et al 2003; Tavares et al 2003), understanding their neurobiologic correlates would be a priority.

Functional imaging studies to date suggest that gambling may activate the brain's dopaminergic reward system. Gambling (Breiter et al 2001) and responses to monetary consequences (Delgado et al 2000; Elliott et al 2000, 2003; O'Doherty et al 2001) in healthy volunteers has been reported to activate the orbitofrontal cortex (OFC), striatum, and limbic areas believed to be part of the extended dopamine reward pathway (Goldstein and Volkow 2002; Kalivas 2001). Salience of a monetary reward has been reported to correlate with caudate and nucleus accumbens activation (Zink et al 2004). It has been postulated that dopaminergic neuron activity in these regions may be involved in the acquisition of associations between salient contextual stimuli and rewarding events

(Drevets 2001, Spanagel and Weiss 1999), which may then lead to sensory stimuli being conditioned as cues for reward expectancy.

The frontal lobes, particularly prefrontal cortices, are believed to be involved in mediating reward expectancy from the direct presentation of rewards or conditioned cues (Hikosaka and Watnabe 2000). The prefrontal cortex has been conceptualized as having two partially overlapping and interconnected neural networks: one involving the OFC believed to be more associated with emotional and motivational aspects of reward expectancy, and one involving the dorsolateral prefrontal cortex (DLPFC) believed to subserve working memory and related cognitive processing of reward expectancy (Hikosaka and Watnabe 2000; Mesulam 2002). Both prefrontal cortices have been reported to be activated by cues after conditioned associations have been acquired (Hugdahl 1998). Findings from functional imaging studies of substance use disorder patients have found increased activation in both the OFC and DLPFC during exposure to substance related cues (Goldstein and Volkow 2002; Heinz et al 2004; Maas et al 1998; Volkow et al 2003; Wexler et al 2001). Similarly, findings from fMRI studies involving healthy volunteers responding to monetary consequences have reported activation in prefrontal and premotor cortices where the authors related the findings to the integration of reward choice salience and preparatory behaviors for obtaining rewards (Elliott et al 2000; Ramnani and Miall 2003).

The only fMRI studies of PG subjects to date (Potenza et al 2003a & 2003b; Reuter et al 2005) have identified relative decreases in OFC and ventromedial prefrontal cortex (VMPFC) activity. In the first, Potenza et al (2003a) compared 10 PG subjects to 11 controls over extended epochs while viewing videotapes designed to simulate

interpersonal interactions as potential emotional and motivational predecessors for gambling craving. Results showed temporally dynamic changes during the viewing of gambling videotapes compared to happy or sad videotapes, with decreased activity found in the OFC, frontal cortical, basal ganglionic and thalamic regions prior to the reported onset of an emotional/motivational response. Decreased ventral anterior cingulate activity occurred during presentation of the most provocative gambling stimuli. The findings were consistent with those reported with decreased impulse regulation (Potenza 2003a), but cue exposure would have been expected to have resulted in increased activity, rather than decreased, in the OFC. Potential compensatory changes or deficits in PG subjects may underlie the findings. The second fMRI study of PG subjects (Potenza 2003b) employed the Stroop Test. The test requires subjects to ignore distractors during target detection and has been shown to activate medial prefrontal, anterior cingulate, and lateral prefrontal cortices in healthy subjects (Coull 1998; Coull and Nobre). The study compared 13 PG subjects to 11 healthy controls and found relatively decreased VMPFC activity in PG subjects. The third study involved 12 PG subjects and 12 matched healthy controls that performed a guessing task previously found to activate the ventral striatum (Reuter et al 2005). The study observed a reduction of ventral striatal and VMPFC activation in PG subjects negatively correlated to gambling severity. The ventromedial prefrontal cortex appears to be more closely aligned with that of the OFC, as deficits in this region have been reported to be associated with decreased response inhibition and a tendency to seek immediate gratification (Bechara et al 1997, 1998). The prior fMRI studies then suggest that PG subjects may be more prone to PG behavior via differential

responses compared to controls to emotional/motivational cues and decreased response inhibition.

Gambling sensory stimuli may be expected to evoke emotional, motivational, cognitive, and spatial aspects of reward expectancy depending on their content. A possibility is that PG subjects preferentially process the visual components of gambling sensory cues for selective attention, spatial processing, and behavior planning. Visual processing has been reported to recruit two separate streams in the brain based on the content of the visual stimulus (for example, see Goodale and Haffenden 2003). Activation of the ventral visual processing stream (striate cortex in occipital lobe to inferotemporal cortex and fusiform gyrus with connection to the ventrolateral prefrontal cortex) has been found with tasks of perception and recognition (Goodale and Haffenden 2003; Ungerleider et al 1998), while activation of the dorsal visual processing stream (striate cortex in occipital lobe to posterior parietal cortex with extensions to the DLPFC) has been associated with spatial processing, task attention, and action preparation (Culham and Kanwisher 2001; Culham et al 1998; Goodale and Haffenden 2003; Marois et al 2000; Shen et al 1999; Ungerleider et al 1998). The dorsal visual processing stream may reflect part of the DLPFC network involving the superior longitudinal fasciculus (Petrides and Pandya 2002).

The current study was undertaken to determine the potential neurobiological correlates of visual gambling cues in PG subjects compared to matched healthy controls. We hypothesized that the presentation of visual gambling cues to PG subjects would result in activation of the DLPFC, including the dorsal visual processing stream.

Methods and Materials:

Participants

Thirteen men with PG and 10 control subjects provided written informed consent and participated in this study approved by the University of Calgary Research and Ethics Board. All participants were recruited from the community by local media and through other gambling research studies conducted at the University of Calgary. Inclusion criteria were the presence of DSM-IV-TR PG (American Psychiatric Association 2003) as per clinical interview, English speaking and male gender. Exclusion criteria were any DSM-IV-TR substance use disorder in their lifetime other than nicotine dependence, any illicit substance use or episode of a mood disorder in the prior 6 months as determined by verbal report (Babor et al 1990), psychotropic medication use in last month, history of psychosis, history of neurologic illness/injury, or inability to tolerate MRI. Three PG subjects were excluded due to active comorbidity, inability to tolerate MRI, or inability to find an adequately matched control subject, resulting in 10 PG subjects and 10 healthy control subjects as participants. Sample size was comparable to previous fMRI studies in addiction (Goldstein and Volkow 2002; Maas et al 1998; Wexler et al 2001), PG (Potenza et al 2003a, 2003b), and normal subjects gambling (Breiter et al 2001). PG subjects and controls were matched for age (\pm 2 years), handedness, gender, ethnicity, and smoking status. Participants were all right-handed. Nicotine dependence was determined by the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al 1991; Pomerleau et al 1994). Smokers were not allowed to smoke for 30 minutes prior to imaging. Gambling histories (including duration of pathological gambling, chosen game(s), and duration of abstinence) were recorded. The Structured Clinical Interview for

DSM-IV – Patient Edition was used for PG subjects and the non-patient version was used for control subjects (First et al 1998). The South Oaks Gambling Screen (SOGS) (Lesieur and Blume 1987) was used to further describe gambling behavior (5 or greater indicative of probable PG). Control subjects were excluded if they scored greater than “1” on the SOGS. All controls required some gambling experience.

Characteristics of PG subjects are described in Table 1. PG subjects and matched controls did not significantly differ in mean age (PG subjects: 39.3 +/- 7.6 years; controls: 39.2 +/- 8.3 years; $t < 1$, $SE < 1$) or smoking status according to mean FTND (PG subjects: 1.2 +/- 2.7; controls = 0.5 +/- 1.1; $t = 1.35$, $p = 0.21$, $SE = 0.52$). One PG subject was nicotine dependent and no control subjects were nicotine dependent. Mean PG criteria were significantly higher for PG subjects than controls (PG subjects: 7.2 +/- 1.8; controls: 0.0 +/- 0.0; $t = 13.00$, $SE = 0.55$, $p < 0.001$). Mean SOGS scores were also significantly higher for PG subjects than controls (PG subjects: 13.9 +/- 2.6; controls: 0.1 +/- 0.3; $t = 16.16$, $p < 0.001$, $SE = 0.85$). One control subject scored “1” on the SOGS based on one gambling experience during his adolescence, however his history otherwise was not indicative of prior or current problem/PG.

Mean duration of PG was 14.1 years (range 5-25 years) and median duration of abstinence from gambling was 5.0 days (range 1-330 days) for PG subjects. Two PG subjects had attained abstinence - one with 180 days of abstinence via voluntary casino exclusion, the other via judiciary involvement and mandated gambling treatment. Two PG subjects had a prior history of major depressive disorder with 2 further having past depressive symptoms but not meeting criteria for a mood disorder. No subjects reported the presence of any other prior or current psychiatric disorders except for 2 PG subjects

reporting a prior history of specific phobia. All PG subjects described prior or current cravings for gambling. Cravings were reported as triggered by access to adequate funds, encountering gambling venues or situations, or affiliation with other gamblers.

Procedures

All fMRI experiments were performed using a 3 Tesla General Electric MR scanner (GE Healthcare, Waukesha, WI). Each subject's head was fixed comfortably inside a standard head coil using foam padding. Liquid crystal display goggles were placed over the eyes and air-driven headphones were placed over the ears (Resonance Technology, Inc., Parthenia, CA). The MR sequence for functional imaging was a 2-shot gradient-recalled echo planar imaging (EPI) sequence (96x96 matrix, zero-filled to 128x128; 24cm field of view, echo time (TE) = 30 ms; repetition time (TR) = 2 sec; 5 mm thick slices with 1 mm gap) with navigator echoes to correct for physiological fluctuations due to respiration (Hu and Kim 1994). Twenty-six image planes were prescribed in an oblique-axial orientation with the aid of sagittal localizer images to encompass the whole head. At the end of the imaging session, a high-resolution 3D (256x256x64) T1-weighted data set was collected for anatomical registration of the functional data. Images were corrected for head motion during post-processing using AIR 5.0 (Woods et al 1992). No subject's data was excluded due to excess motion (>2mm). The time course of image pixel intensity was subjected to a high-pass filter (cutoff = 120s) to remove low-frequency oscillations inherent in EPI data. No spatial filtering was applied.

Functional MR images were acquired throughout each of 3 experimental runs using a block design. Each 240-second run consisted of 4 presentations of 30 seconds of nature video followed by 30 seconds of gambling sensory stimuli. This block design was used to permit the saliency of a given cue to induce activity, which may take several seconds to occur. Rank order effects were limited by using different gambling and nature videos during each 30-second segment. No video sequences were ever repeated. Three different sets of visual gambling cues were selected to test the effect of viewing scenes of casino gambling activity, casino venues, and specific game play as it had not been reported previously whether or not different cue types for gambling are processed differently. The first 240-second run (Casino Gambling Run) displayed 4 novel 30-second segments of individuals gambling in casino settings playing blackjack, craps, roulette, and slot machines/video lottery terminals (VLTs) and receiving cash payouts. The video sequences focused on action in the casino rather than on specific strategic game play. The second 240-second run (Gambling Venues Run) displayed 4 novel 30-second segments of gambling venues involving the exteriors of Las Vegas casinos. The third 240-second run (VLT Run) displayed 4 novel 30-second segments of a VLT being played where viewers could observe the strategies being used. The nature video was also novel in each 30-second segment and consisted of wildlife and nature scenes.

Subjects' craving for gambling was assessed via a 7-point Likert-type scale (0 = absent to 7 = maximal desire to gamble) prior to the imaging session and at the end of the each 240-second run. Although there was no psychometrics for this type of scale, it was chosen as it would be brief and would allow subjects to remain still in the fMRI over the entire imaging session for best image acquisition. A pre-imaging discussion occurred to

emphasize that subjective craving reports were to be based upon the desire, urge, or motivation to gamble evoked by the stimuli only. As it was expected that craving might evolve over time and to further stimulate their cravings, subjects were informed prior to the MRI that they would have the opportunity to gamble after all video sequences were complete during acquisition of the high resolution structural images. Subjects played a slot machine game in the MRI. Subjects' heart and respiration rates were continuously monitored and recorded during each video segment throughout the session using a MR-compatible pulse oximeter attached to the middle finger of the left hand and respiratory bellows strapped around the lower rib cage, respectively.

Data Analysis and Statistical Considerations

Two separate individuals (BG, JE) performed the data analysis and were blinded to subject diagnosis. The time course of intensity of each brain pixel over all runs and the expected signal time course, derived from the convolution of the box-car presentation of the stimuli with an ideal hemodynamic response to a 1-second stimulus (Birn et al 2002), were subjected to a correlational analysis using *Stimulate* (CMRR, University of Minnesota). Pixels exhibited a correlation coefficient of 0.3 (equivalent $p=0.05$ with 42 degrees of freedom in a pixel's time course) were considered as significantly "activated" by the gambling video. The average percentage increase in MR signal in response to the gambling video over the course of the experiment for each significant pixel was recorded using *Stimulate*. Image data was transformed to the standardized stereotaxic space of Talairach and Tournoux (Talairach and Tournoux 1988) for group analysis. Due to the relatively small sample sizes, the percentage increases for each brain pixel of each

participant were subjected to the Mann-Whitney U-Test ($U_{\text{critical}} = 64$ for a significance level of 0.05, corrected for multiple comparisons) to determine if brain regions were activated for each group. Clustering of activated pixels was performed to achieve a corrected $z > 2.3$ for each cluster (Forman et al 1995). Activated clusters were identified by Talairach coordinates and activation volumes were then calculated for each cluster. An additional higher-level t-test was performed to determine activation volume differences of brain regions between groups (significance level of 0.05, corrected for multiple comparisons). Demographic data were compared between groups by univariate statistical analysis. The craving and physiologic data were compared using multivariate Analysis of Variance (ANOVA).

In a post-hoc region of interest analysis, the percentage increase in MR signal was compared within groups in a trend analysis to determine if cue type modulated brain activity level.

Results

Craving and Physiologic Data

Mean values for craving and physiological responses are presented in Table 2. Results for craving data indicated that mean baseline subjective craving for PG subjects was significantly greater than controls ($t=2.24$, $p=0.05$, $SE=0.45$), as was the mean change in subjective craving ($t=3.48$, $p=0.007$, $SE=0.55$). Note that this effect was attenuated by the 2 abstinent PG subjects, who reported no craving response. PG subjects and controls subjectively reported different levels of interest in the audiovisual stimuli. Controls reported the most interest for the Gambling Venues Run, less for the Casino

Gambling Run and least for the VLT Run. By contrast, PG subjects reported little interest in the Gambling Venues Run, some for the Casino Gambling Run, if the action matched their preferred gambling type, and the most interest for the VLT Run, particularly relating to the gambling strategies used.

A 2 (patient) x 2 (stimuli) repeated measures analysis of variance ANOVA revealed that mean heart rates were not significantly different across stimuli conditions ($F(1,17)=1.77$, $p=0.20$, $MSE=2.24$). Mean respiratory rates were also not significantly different across stimuli ($F(1,17)<1$, $p=0.82$, $MSE<1$). These results suggest that the differences in fMRI findings between subject groups are not attributable to gross physiologic parameters.

fMRI:

PG subjects and controls showed significant activity in several overlapping regions in response to the gambling stimuli (see Table 3). However, significantly greater activity was identified in the right DLPFC including the right inferior frontal gyrus ($t(9) = 2.86$, $p=0.02$) representing Brodmann Area (BA) 44 and the right medial frontal gyrus ($t(9) = 2.63$, $p=0.03$) representing BA 9. The greater activity in the DLPFC related to increased activity in the PG subjects alone (see Table 3) as displayed in Figures 1 and 2. Additional findings were of increased activation of the right parahippocampal gyrus ($t(9) = 2.88$, $p=0.018$) and left fusiform gyrus ($t(9) = 2.42$, $p=0.039$) representing BA 19 in PG subjects compared to controls. Control subjects demonstrated increased activity in the right parahippocampal gyrus, but PG subjects demonstrated proportionately greater activity as measured by volume and cluster Z (see Table 3 and Figure 3). Greater left

fusiform gyrus activity in PG subjects related to increased activity in PG subjects alone (see Table 3 and Figure 3).

Post-hoc trend analysis of all regions, as reported in Table 3, revealed a dissociation in brain activity based upon cue type (see Figures 4 and 5). PG subjects exhibited *increasing* activation volume in the dorsal visual processing stream, including BA 7 involving the right precuneus ($F(1,9)=5.08$, $p=0.05$, $MSE=7742.35$) and left precuneus ($F(1,9)=6.15$, $p=0.04$, $MSE=613.50$) as well as BA 40 involving the right inferior parietal lobule ($F(1,9)=8.67$, $p=0.01$, $MSE=6604.26$) as cue type was changed from Gambling Venues to Casino Gambling to VLT. By contrast, controls displayed *decreasing* activation volume in the ventral visual processing stream, including BA 19 involving the right medial occipital gyrus ($F(1,9)=7.18$, $p=0.03$, $MSE=50686.45$), BA 17 involving the right cuneus ($F(1,9)=5.82$, $p=0.04$, $MSE=11447.66$), right lingual gyrus ($F(1,9)=5.99$, $p<0.04$, $MSE=24879.11$), and BA 18 involving the left lingual gyrus ($F(1,9)=5.39$, $p=0.05$, $MSE=11755.52$) as cue type was changed from Gambling Venues to Casino Gambling to VLT. No other trends were significant.

Discussion:

PG subjects in comparison to matched controls exhibited increased activity in the right DLPFC, right parahippocampal region, and left occipital cortex when exposed to visual gambling sensory cues. Findings were associated with a significantly greater baseline craving and mean change in craving for gambling in PG subjects despite the stimuli not specifically matching their preferred game(s) of choice. PG subjects activated the dorsal visual processing stream in response to viewing a VLT being played, whereas

controls activated the ventral visual processing stream when viewing gambling venues. Brain regions of activation in PG subjects compared to controls predominantly involved regions believed to represent the DLPFC network (Mesulam 2002). Together the findings suggest that visual gambling sensory cues are preferentially recognized by PG subjects as being salient for attention, reward expectancy, and behavior planning for attaining rewards.

Activation of the DLPFC network suggests that the cues involved the use of working memory (Barch and Buckner 2003), which is thought to play an important role in coding external events into internal representations and volitional scanning enabling contents of consciousness to be selected deliberately, rather than reflexively, by events in the environment (Mesulam 2002). The predominantly right-sided DLPFC findings in this study likely relate to the right hemispheric specialization for visuospatial tasks and the lack of a verbal component to the stimuli (Barch and Buckner 2003). However, the predominantly right-sided findings may also relate to a right-sided superiority in human conditioning, where the right hemisphere is more resistant to extinction (Hugdahl 1998) or the preferential activation of right prefrontal regions during memory retrieval (Cabeza and Nyberg 2002; Tulving et al 1994).

The DLPFC is believed to be bi-directionally linked with other distant cortical areas to allow the interpretation of sensory stimuli to be linked to prior experiences and the generation of goal-directed action (Goldman-Rakic and Leung 2002; Petrides and Pandya 2002). The findings of activation in the DLPFC and parahippocampus may suggest that contextual cues for gambling result in memory retrieval based on prior experience with associated modulation of attention and behavior potentially interpreted as

a craving response. Another possibility, though, is that parahippocampus activity may relate to encoding of information or activity in the ventral visual processing stream involving its occipitotemporal connections (including to the parahippocampus) for object perception and recognition relating to PG subjects' prior experiences (Petrides and Pandya 2002). However, greater activity in the ventral visual processing stream of PG subjects compared to controls was not found in the trend analysis (Fig. 5). The segregated findings based on subject and cue type also argue against the findings being secondary to time/order effects (where global effects may have been expected), although randomizing the order of the cues would have further supported this assertion. Unfortunately, the correlational nature of the fMRI findings in the current study prevent more definitive statements being made as to the basis of the parahippocampus activation beyond these speculations.

The DLPFC is also believed to be reciprocally linked with the posterior parietal cortex via the superior longitudinal fasciculus allowing the focusing of attention within different parts of space (Petrides and Pandya 2002). The posterior parietal cortex appears to participate in allocating attentional resources, transforming sensory data into the generation of movements and the selection of movements for execution (Dorris and Glimcher 2004). The activation of parietal structures found in the trend analysis of PG subjects may then suggest that visual gambling sensory cues, particularly of specific game play, initiate preferential allocation of attentional resources to aspects of game play with preparation for action potentially indicative of a craving response. This would correlate also with the subjective reports of PG subjects in this study.

Differential brain activation in PG subjects was not correlated with measures of physiologic response. The lack of physiologic response to gambling cues could be interpreted as incongruent with the found change in craving, but is not atypical of gambling studies where laboratory simulations have been attempted (Anderson and Brown 1984) and where there is limited expectancy for winning money (Ladouceur et al 2003) or experiencing money being won (Coventry and Hudson 2001).

Prior functional imaging studies involving cocaine dependent subjects found increased activity in the DLPFC corresponding to the anticipation of immediate drug self-administration and self-reports of subjective craving (Goldstein and Volkow 2002). Although the PG subjects in this study reported increased craving for gambling, it is not clear whether the differential brain activity was related to craving, a conditioned response, both, or neither. It is recognized that craving is a complicated phenomena that evolves over time and requires subjective report potentially influenced by elements in and out of conscious awareness (Goldstein and Volkow 2002). Although attempts were made to assess craving based upon cue-elicited desire, urge, or motivation to gamble, it cannot be guaranteed that subjective responses may have been influenced by other factors (e.g., mismatch between preferred game and that in the video, conditioned behavior, and/or desire to present well in context of abstinence). This may explain why the craving responses of PG subjects varied. A future study may improve on this by involving PG subjects who all prefer the same type of gambling to match cues to their preference and determine, prior to imaging, that all subjects view these cues as sources for craving and/or conditioned gambling behavior.

A potential confound in the study that may have limited observed differences between PG and controls could have emanated from carryover effects from telling subjects that they would be able to gamble after the video sequences. This was done in the attempt to maximize differences in regional brain activation as been found previously (Volkow et al 2003), but may have inadvertently led to sustained activation during exposure to the neutral stimuli by memories evoked by the gambling cues.

In addition, baseline cravings varied but were significantly different between PG subjects and controls. The elevated baseline cravings likely limited the ability of subjects to describe further increases in cravings, decreasing the differences between controls and PG subjects in measured craving responses. Baseline cravings may have also resulted in carryover effects that could have confounded the fMRI results by limiting differences found between neutral and activating stimuli in the PG subjects. Baseline cravings may have been indicative of ongoing reward expectancy with the PG behavior and thoughts about gambling being conditioned. This would be consistent with the long duration of PG (mean = 14.1 years) in the PG subjects sampled. The long duration of PG may also explain why activity in the DLPFC was found rather than in the OFC beyond that relating to the audiovisual content. It has been suggested that the OFC is involved first in reward expectancy owing to its close affiliation with reward pathways, whereas the DLPFC may be involved later to integrate motivational and cognitive operations (Hikosaka and Watnabe 2000). If this is so, DLPFC activity may be a marker of established conditioned (or dependent) behavior. It is unclear how long DLPFC activity elicited by cue exposure could persist even in the context of abstinence. Thus, the 2 abstinent subjects in this study may or may not have confounded the fMRI results, although ideally, the study would

have been improved if it had only involved active PG subjects with cravings evoked by visual cues. If there was an effect, it would have been expected to reduce the differences found between subjects and controls. A separate analysis of the abstinent subjects was not done as 2 subjects would be too small to identify meaningful results. Future work might attempt to examine abstinent subjects or compare subjects based on their duration of PG to see if their activation patterns differ.

The differences between OFC and DLPFC in regards to their roles in reward expectancy may explain the difference in findings between the current study and the prior fMRI study of PG subjects and urges for gambling (Potenza et al 2003a). One of the major differences between the studies was in regards to how they attempted to evoke urges or cravings for gambling. The current study used visual gambling sensory cues whereas the prior study presented predominantly an interpersonal simulation to evoke emotional and motivational predecessors to gambling with provocative gambling footage presented at the end of the audiovisual sequences. The cognitive and spatial stimuli from the current study would have preferentially involved the DLPFC, whereas the emotional and motivational predecessors of the prior study would have preferentially involved the OFC and its closely affiliated limbic/subcortical brain structures. Thus, PG subjects may activate different prefrontal cortex networks depending on cue type. Gambling sensory cues may evoke reward expectation mobilizing attention, spatial processing, and preparatory behaviors, while emotional and motivational predecessors may be more directly linked to reward expectancy by their closer association to reward experience. The former may associate cues to recollected prior gambling experiences, and the latter may generate internal emotional states that alter subsequent decision making. It is not known

whether response patterns overlap, or if they are representative of different PG subsets or duration of PG. In retrospect, the addition of a cue involving emotional predecessors to gambling may have helped determine this. The extent to which differences in neural activation patterns reflect differences in experience, abstinence duration, and potential subsets of pathological gamblers requires further examination.

Ability to generalize the results to all PG subjects may have been limited by the use of a community sample and excluding subjects with a lifetime history of a substance use disorder (other than nicotine dependence) or any illicit substance use in the last 6 months. PG is highly comorbid with substance use disorders (Crockford and el-Guebaly 1998). Although the prevalence of comorbid major depressive disorder and nicotine dependence in our sample was lower than that reported in other studies (Crockford and el-Guebaly 1998; Petry and Oncken 2002), it is relative to studies using community samples where comorbid substance dependence (other than nicotine) is controlled for (Crockford and el-Guebaly 1998; Smart and Ferris 1996). The exclusion criteria were used to remove the potential confounding effect of prior or current substance use on induced brain activity (Goldstein and Volkow 2002) and its potential for altering gambling behavior (Brunelle et al 2003; Zack and Poulos 2004). Thus, although the ability to generalize findings to highly comorbid treatment-seeking samples may be reduced, there may be greater validity in our results being attributable to PG alone.

In conclusion, PG subjects compared to matched controls exhibited increased activity in the right DLPFC when exposed to gambling sensory cues. Tentatively, the findings from the current study and prior work suggest that monetary rewards from gambling activate brain reward circuitry, which may result in the salience of gambling

being associated with contextual cues that are processed by potentially different aspects of the prefrontal cortex for reward expectancy. Future work should attempt to replicate and extend the present study's findings by evaluating subsets of PG subjects based upon their motivations for gambling and chosen games as well as incorporate gambling tasks.

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Tables:

Table 1: Characteristics of PG Subjects

Age (Years)	SOGS	PG Criteria	PG duration (Years)	Game (a)	Mood History (b)	Abstinence (Days)	Craving Change (c)
31	13/20	7/10	9	BJ	-	28	1.7/7
38	17/20	8/10	12	VLT	+	7	3.3/7
39	14/20	5/10	18	VLT, S	+	3	3.2/7
31	14/20	9/10	18	Craps,R,S	MDD	2	3.0/7
41	15/20	10/10	6	VLT,S	-	2	1.3/7
48	13/20	6/10	24	VLT	MDD	7	5.3/7
54	12/20	6/10	25	BJ	-	1	3.4/7
35	10/20	5/10	14	Craps	-	180	0/7
32	12/20	7/10	10	BJ,Poker	-	3	2.7/7
43	19/20	9/10	5	VLT	-	330	0/7

Legend:

(a) Game: VLT = video lottery terminal / slots, BJ = blackjack, R = roulette, S = sports betting

(b) Mood History: “-“ = < 3 prior depressive symptoms, “+” = 3 or more prior depressive symptoms,

“MDD” = prior major depressive disorder

(c) Craving change from baseline as per 7-point Likert-type scale over 3 fMRI runs

Table 2: Mean Subjective Craving and Physiological Response Values in PG Subjects and Controls

	PG Subjects(N=10)		Controls (N=10)		Significance
	Mean	SD	Mean	SD	
Subjective Craving Data					
Baseline Craving	1.00	1.41	0.0	0.0	p=.05
Change in Craving	2.50	1.67	0.57	0.75	p=.007
Change in Craving (excluding abstinent subjects)	3.12	1.17	0.57	0.75	p<.001
Physiological Data					
Heart Rate	69.39	8.50	62.74	6.50	p>.05
Respiratory Rate	16.81	0.91	17.06	0.82	p>.05

Table 3: Talairach Coordinates of Significant Brain Activity in Pathological Gamblers and Controls.***p<0.05**

Region of Activation	Brodmann Area	Talairach Coordinates x, y, z	Gamblers		Controls	
			Activated volume (cm ³)	cluster Z	Activated volume (cm ³)	cluster Z
Right Precuneus (RP)	7	-9, -63, +48	1.65	3.1	0.37	2.4
Left Precuneus (LP)	7	+5, -63, +46	0.72	2.8	0.37	2.4
Right Inferior Parietal Lobule (RIPL)	40	-40, -60, +45	8.93	3.1	6.17	2.8
Left Inferior Parietal Lobule (LIPL)	40	+42, -60, +44	9.21	3.1	3.77	2.8
Right Inferior Frontal Gyrus (RIFG)*	44	-50, +13, +24	1.90	3.1	—	—
Right Middle Frontal Gyrus (RMFG)*	9	-8, +58, +18	0.30	2.4	—	—
Right Medial Occipital Gyrus (RMOG)	19	-28, -88, +18	16.48	3.1	12.69	3.1
Left Medial Occipital Gyrus (LMOG)	19	+32, -90, +20	17.31	3.6	11.92	3.1
Right Cuneus (RC)	17	-16, -82, +8	5.54	3.6	3.67	2.8
Left Cuneus (LC)	17	+10, -76, +6	1.98	3.1	2.90	2.8
Right Lingual Gyrus (RLG)	18	-12, -62, -2	5.53	3.6	4.55	3.1
Left Lingual Gyrus (LLG)	18	+10, -70, 0	5.26	3.1	4.35	2.8
Right Inferior Occipital Gyrus (RIOG)	18	-36, -88, -4	0.87	2.8	1.00	2.8
Left Inferior Occipital Gyrus (LIOG)	18	+32, -82, -6	0.72	2.4	0.86	2.4
Right Parahippocampal Gyrus (RPG)*	19	-20, -45, -4	1.59	3.1	0.44	2.4
Right Fusiform Gyrus (RFG)	19	-24, -62, -10	1.91	2.8	0.63	2.4
Left Fusiform Gyrus (LFG)*	19	+20, -66, -12	1.98	2.8	—	—

Figure Legends:

Figure 1: Three-dimensional rendered volumes of MR data showing significant overall increased cortical activity ($p < 0.05$) differences between nature and gambling video viewing predominantly in the right hemisphere (RH) versus the left hemisphere (LH) in (a) Pathological Gamblers and (b) Controls.

Figure 2: Talairach group maps (horizontal slice orientation) of MR data showing significantly increased brain activity ($p < 0.05$) predominantly in the right hemisphere (RH) versus the left hemisphere (LH) of the dorsolateral prefrontal cortex (Brodmann's Areas [BA] 44 & 46) in (a,d) Pathological Gamblers, (b,e) Controls, and (c,f) significant difference between the groups.

Figure 3: Talairach group maps (horizontal slice orientation) of MR data showing significantly increased brain activity ($p < 0.05$) in parahippocampal region (PH) in the right hemisphere (RH) and fusiform gyrus (FG) in the left hemisphere (LH) in (a) Pathological Gamblers, (b) Controls, and (c) significant difference between the groups.

Figure 4: Regions within the dorsal visual processing stream showing (a) significantly increasing activity ($p < 0.05$) in the left & right precuneus (LP & RP) and left & right inferior parietal lobules (LIPL & RIPL) of PG subjects as a function of cue type, with (b) no significant increase for controls.

Figure 5: Regions within the ventral visual processing stream showing (a) no significant increases in brain activity for PG subjects as a function of cue type, and (b) significant increases in the activity of right medial occipital gyrus (RMOG), right cuneus (RC), left & right lingual gyri (LLG & RLG), and right fusiform gyrus (RFG) of controls.

Figure 1:

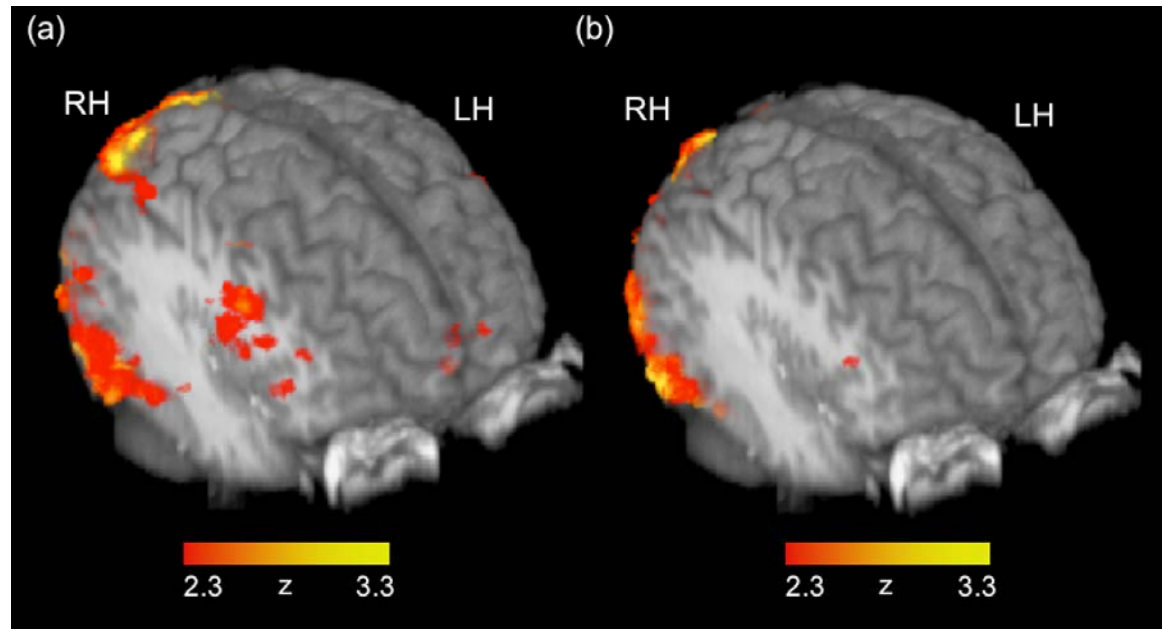


Figure 2:

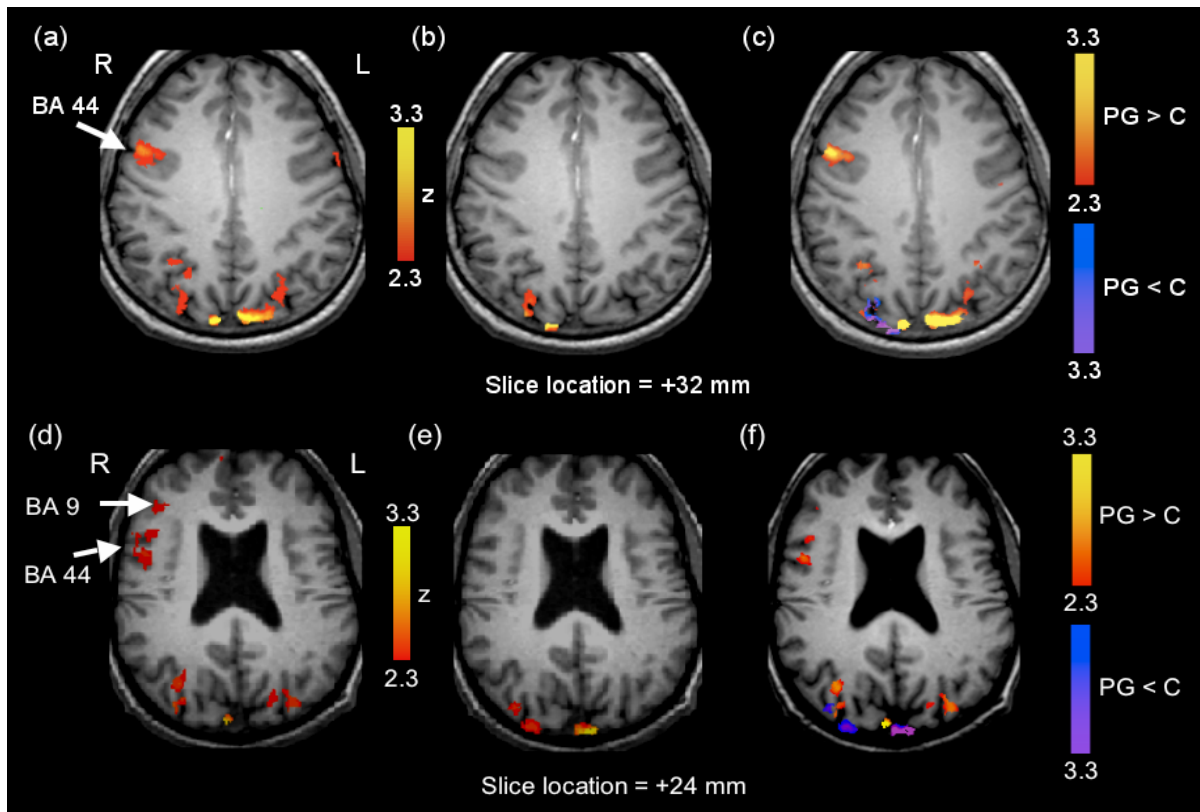


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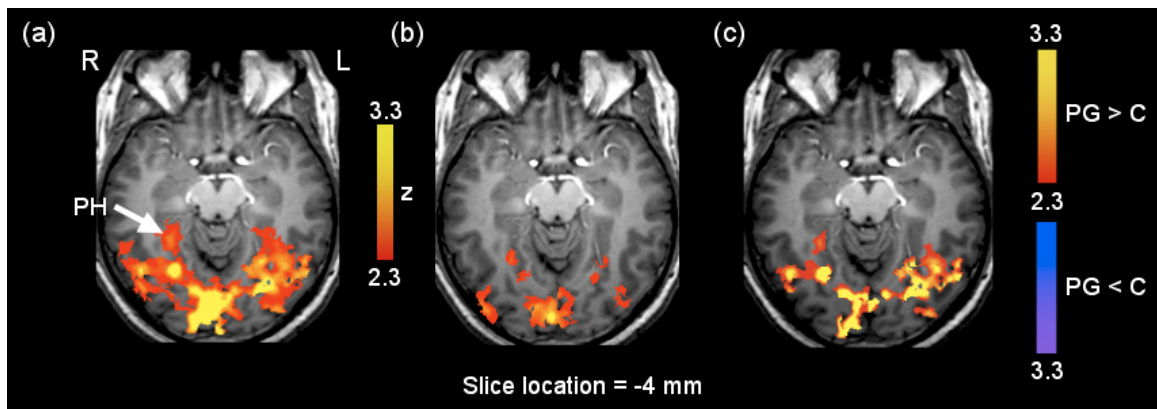


Figure 4:

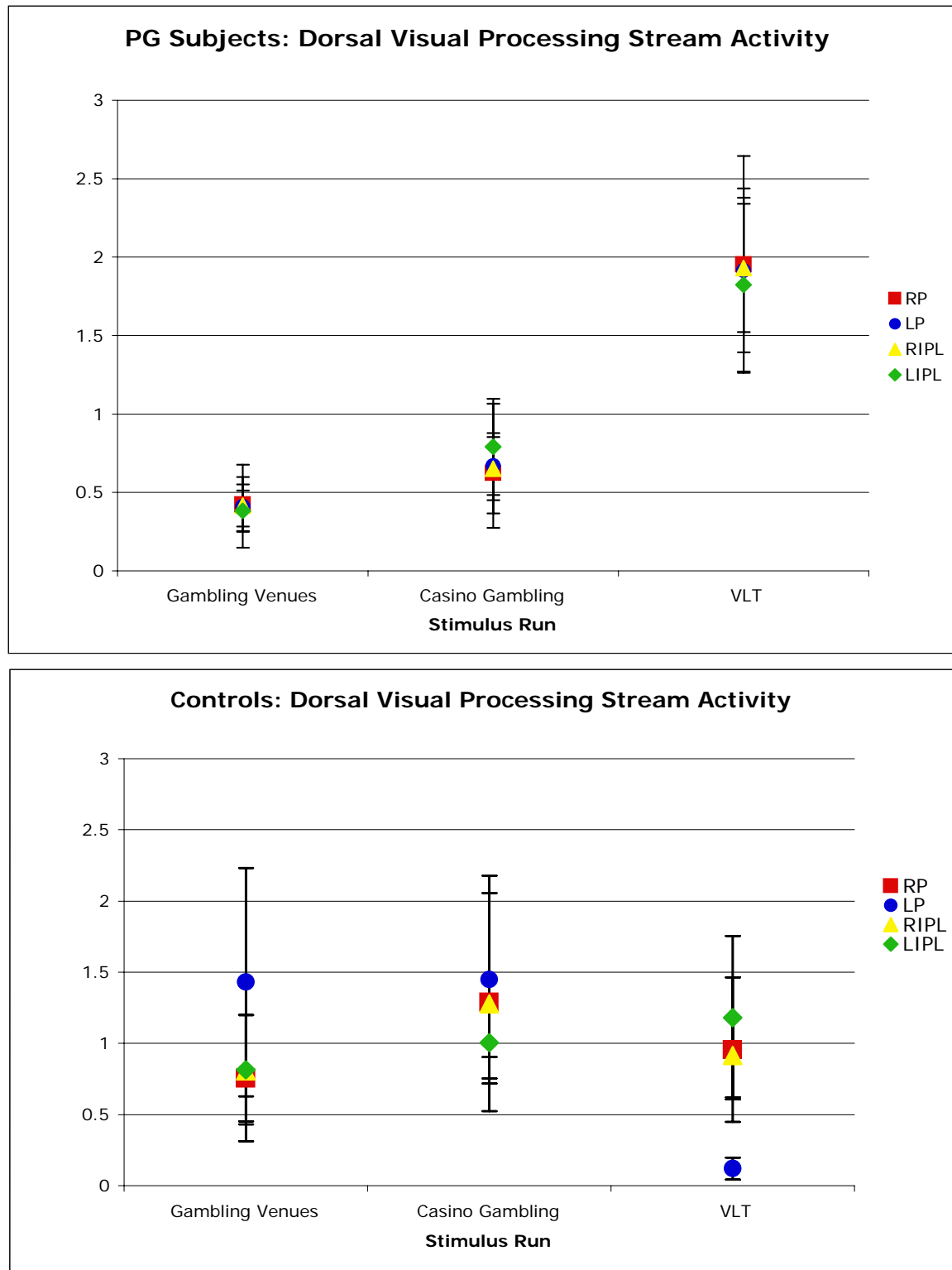


Figure 5:

