

Diminished Frontostriatal Activity During Processing of Monetary Rewards and Losses in Pathological Gambling

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Background: Mesocorticolimbic neurocircuitry and impulsivity have both been implicated in pathological gambling (PG) and in reward processing. However, the neural underpinnings of specific phases of reward and loss processing in PG and their relationships to impulsivity remain only partially understood. The present functional magnetic resonance imaging study examined brain activity associated with different phases of reward and loss processing in PG. Given an inverse relationship between ventral striatal recruitment during anticipation of monetary rewards and impulsivity in alcohol dependence, the current study explored whether a similar association might also be present in PG.

Methods: Fourteen adults with PG and 14 control comparison participants performed the Monetary Incentive Delay Task to identify brain activation changes associated with reward/loss prospect, reward/loss anticipation, and reward/loss notification. Impulsivity was assessed separately using the Barratt Impulsiveness Scale.

Results: Relative to the control comparison group, the PG group exhibited significantly reduced activity in the ventromedial prefrontal cortex, insula, and ventral striatum during several phases, including the prospect and anticipation phases of both gains and losses. Activity in the ventral striatum correlated inversely with levels of impulsivity in PG participants, consistent with prior findings in alcohol dependence.

Conclusions: Relatively decreased activity in corticostriatal neurocircuitry during multiple phases of reward processing suggests consistent alterations in neurocircuitry underlying incentive valuation and loss prediction. Together with findings in alcohol dependence, these results suggest that impulsive tendencies in addictions may be reflected in diminished ventral striatal activations to reward anticipation and may represent targets for treatment development in addictions.

Key Words: fMRI, gambling, incentive, insula, ventral striatum, vmPFC

Pathological gambling (PG) shares clinical features with substance addictions, and both demonstrate similar alterations in motivational and reward neurocircuitry (1–7). Both PG and substance-dependent individuals show differences in neural responses to drug and monetary reward cues (2,6,8,9). Relatively little is known, however, about the neural correlates of specific temporal phases of reward and loss processing in PG. In nonaddicted adults, investigations into the neural underpinnings of reward processing have identified distinct anticipation and outcome phases, with reward anticipation linked to activation of the ventral striatum (VS) and reward notification or outcome linked to activation of the ventromedial prefrontal cortex (vmPFC) (10–14). Neural responses during anticipation are significant, as they are temporally ordered to influence decision-making processes and behavior (15). Different patterns of corticostriatal activations during anticipatory phases of reward processing are observed in substance-dependent patients relative to healthy adults. For example, persons with alcohol dependence show relatively diminished VS activation during reward anticipation (8). Furthermore, this activation correlates inversely with

self-reported impulsivity (8), the tendency to act quickly without planning or regard for negative consequences (16,17), which has been linked to propensities to develop addictions and to addiction treatment outcomes (8,18–20).

Neuroimaging studies indicate diminished activation of corticostriatal circuitry in PG. Diminished vmPFC activation has been reported in PG during cognitive control (21), gambling cue presentation (2), simulated gambling (3), and among those with co-occurring substance abuse/dependence during risk/reward decision making (4). Relatively diminished VS activation has also been observed in PG during simulated gambling (3) and in response to gambling-related cues (6). Among individuals with Parkinson's disease and impulse control disorders (including PG) as compared with persons with Parkinson's disease alone, diminished VS activation occurs during risk taking, with differences in perfusion also observed (22). Reduced insula activity has been reported in PG individuals viewing gambling cues (6). In nonaddicted individuals, insula activation is implicated in loss prediction and financial risk taking (23–25). Alterations in reward and loss processing circuitry appear particularly relevant to PG, as they may generate misrepresented valuations of rewards or punishments and promote risky choices and continued gambling (26,27). For example, some neurophysiological data suggest hypersensitivity to reward following losses in problem gamblers (28). To date, however, PG studies examining monetary incentives have included paradigms that do not fully disambiguate specific variables such as probability, response preparation, certainty, guessing, and choice—all of which may differentially contribute to reward processes.

No functional magnetic resonance imaging (fMRI) study in PG has examined the neural correlates during different phases of reward and loss processing, thus limiting understanding of temporal fluctuations attributable to aspects of incentive processing in PG. A widely used fMRI task for investigating monetary reward

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Received Jul 20, 2011; revised Jan 4, 2012; accepted Jan 5, 2012.

Table 1. Characteristics of PG and CC Participants

	PG	CC	Test Statistics
<i>n</i>	14	14	
Male/Female	10/4	10/4	
Current Smoker	6	2	$\chi^2 = 4.76, df = 1, p < .05$
Age (SD)	35.8 (11.7)	37.1 (11.3)	ns
IQ – Shipley (SD)	102.8 (12.4)	106.5 (13.2)	ns
SOGS (SD)	12.6 (3.5)	.3 (.6)	$F(1,26) = 169.28, p < .001$
BIS-11 Total Score (SD)	68.07 (12.26)	59.13 (12.08)	$F(1,25) = 3.64, p = .1$
Attention Subscale (SD)	16.36 (4.47)	13.92 (3.88)	$F(1,25) = 2.27, p > .1$
Motor Subscale (SD)	25.14 (4.54)	22.52 (4.24)	$F(1,25) = 2.41, p > .1$
Nonplanning Subscale (SD)	26.57 (5.45)	22.69 (5.19)	$F(1,25) = 3.58, p = .1$

BIS-11, Barratt Impulsivity Scale version 11; CC, control comparison; IQ, intelligence quotient; PG, pathological gambling; SD, standard deviation; SOGS, South Oaks Gambling Screen.

processing is the Monetary Incentive Delay Task (MIDT), which can parse anticipatory and outcome phases (8,11,12,15,29,30). This task has recently been modified to model two distinct anticipatory phases relating to prospect (A1) and anticipation of notification (A2) of reward/loss (18). This MIDT structure effectively separates anticipatory processes from choice and further parses neural activity associated with motor preparation/demands. In this way, the modified MIDT provides an ordered framework to examine the neurobiological substrates underlying specific aspects of reward and loss processing in PG. In accordance with evidence for ventral striatal and vmPFC recruitment during reward anticipation and outcomes, respectively, and diminished activation of these regions in PG during simulated gambling, we hypothesized that the PG group would demonstrate relatively diminished VS activation during the A1 and A2 phases and relatively diminished activation of vmPFC during the outcome phase of the MIDT. Given insular contributions to financial risk taking and loss prediction (23), we hypothesized relatively reduced insula activity during loss processing in PG. Given similar neurobiological contributions to substance and nonsubstance addic-

tions (1–7) and findings in alcohol dependence (8), we hypothesized that VS activity during the anticipatory phase would inversely correlate with self-reported impulsivity in the PG group.

Methods and Materials

Participants

Participants were 14 individuals who met criteria for PG and 14 control comparison (CC) participants (demographic and self-reported measures are displayed in Table 1). Sample characteristics are more fully described in Supplement 1. All participants except one CC individual completed the Barratt Impulsivity Scale version 11 (BIS-11) (31). The BIS-11 is a valid and reliable measure of impulsivity that factors into motor, attention, and nonplanning subscales (31). Urine toxicology at the time of scanning verified that all individuals were free of illicit substances. All participants provided written informed consent. The study was approved by the Yale Human Investigations Committee.

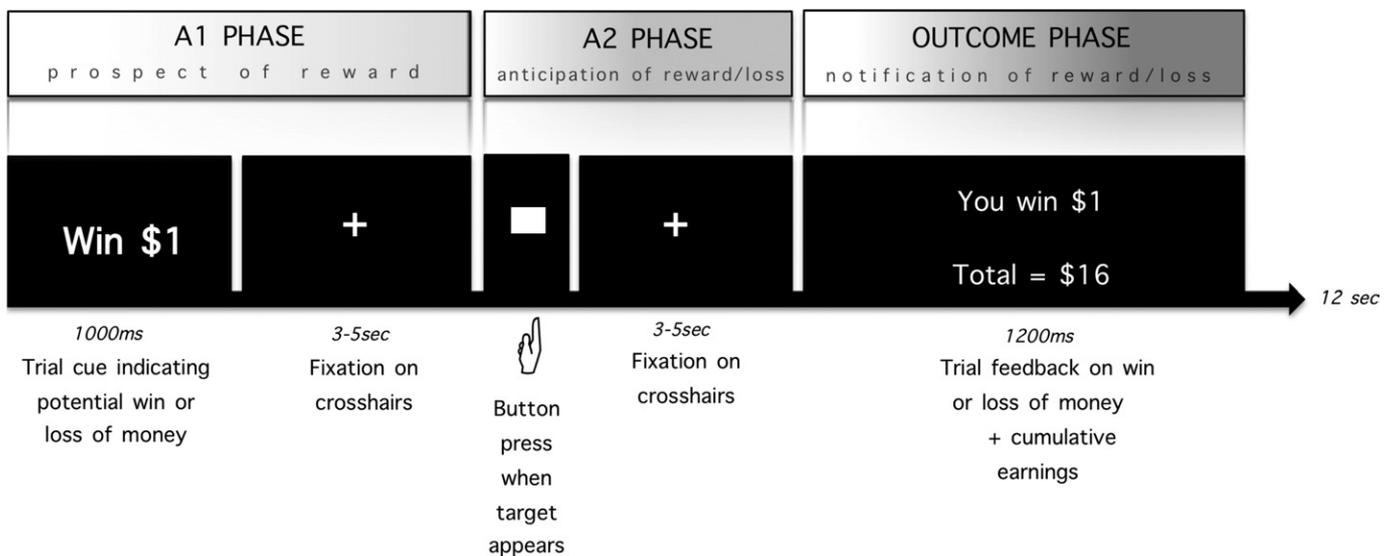


Figure 1. Monetary Incentive Delay Task adapted from Knutson *et al.* (11), described in Andrews *et al.* (18). Participants first view an incentive cue signaling the potential to win or lose money and then fixate on a + (prospect of reward phase; A1). Then, in the anticipation of reward/loss (A2) phase, a target appears. Participants win (or avoid losing) money by pressing a button before the target disappears. Participants then wait for feedback notifying whether they have won or lost the trial (A2). In the outcome phase, participants receive feedback on whether they have won or lost the trial and their cumulative earnings. Task difficulty (length of target presentation) is based on reaction times collected during a prescan practice session, such that participants win on ~66% of trials.

Table 2. Group Differences During MIDT Trials

MIDT Phase	Structure	BA	Left/Right	MNI Coordinates				F/t Value
				x	y	z	k	
A1 Winning	mPFC/vmPFC/ACC/ventral striatum	9/10/24	L	−9	45	24	348	−4.92
	Inferior frontal gyrus	45	L	−51	27	−6	110	−3.70
	Precuneus	7	L	3	−54	54	47	3.22
A1 Losing	mPFC/ACC	9	L	−12	45	21	142	−4.48
	Inferior frontal gyrus/insula	45/47	L	−51	30	−6	107	−4.05
	Ventral striatum/vmPFC	10/11/25	L	−18	18	−6	103	−3.84
A2 Winning	ROI: Ventral striatum	−	R	10	12	−11	123	$F(1,26) = 4.91$
	vmPFC/ventral striatum	11	R/L	3	24	−15	99	−4.10
A2 Losing	ROI: Ventral striatum	−	R	10	12	−11	123	$F(1,26) = 4.72$
	ROI: Ventral striatum	−	L	−10	12	−11	123	$F(1,26) = 4.57$
Winning Outcome	mPFC/ACC/vmPFC	9/32/24/10	L/R	9	33	−3	238	−4.03
	Posterior cingulate/hippocampus	30	L	−18	−51	9	119	−3.83
Losing Outcome	Superior temporal gyrus/insula	22	R	48	−9	−9	116	−4.65
	Middle occipital gyrus/posterior cingulate/cuneus	18	R	24	−81	−9	806	−4.39
	Superior parietal lobule	7	R	27	−57	54	230	−4.29
	Precentral gyrus	6	L	−60	0	39	110	−4.24
	Middle/superior temporal gyrus/insula	37	L	−42	−60	3	367	−4.16
	Superior frontal gyrus	8	L	−18	18	45	353	−3.49
	Superior frontal gyrus	8	L	−6	48	48	148	−3.39
	Middle frontal gyrus	10	R	21	60	12	120	−3.19
	ROI: Ventral striatum	−	L	−10	12	−11	123	$F(1,26) = 4.35$

A1, prospect of reward; A2, anticipation of reward/loss; ACC, anterior cingulate cortex; BA, Brodmann area; L, left; MIDT, Monetary Incentive Delay Task; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; R, right; ROI, region of interest; vmPFC, ventromedial prefrontal cortex.

Monetary Incentive Delay Task

All participants completed the MIDT (Figure 1). The task and experimental methods are described elsewhere (18) and in Supplement 1.

fMRI Acquisition and Analysis

Images were obtained using a Siemens 3 Tesla scanner (Trio; Siemens AG, Erlangen, Germany) at the Yale Magnetic Resonance Research Center at the Yale University School of Medicine. Image acquisition and analysis methods are detailed further in Supplement 1. Functional images were preprocessed using SPM5 (Wellcome Functional Imaging Laboratory, London, United Kingdom), normalized to the Montreal Neurological Institute template, and smoothed with a 6-mm kernel full-width at half maximum. First-level modeling was conducted using robust regression (32) to reduce the influence of strong outliers (33). Motion parameters and high-pass filter parameters were included as additional regressors of no interest. NeuroElf analysis package (www.neuroelf.net) was used for second-level random effects analysis. Correction for multiple comparisons was conducted using Monte-Carlo simulation (e.g., AlphaSim), using a combined voxelwise and cluster thresholds to result in a family-wise error rate of 5%. To examine the effects of task on brain activation, we contrasted: 1) anticipation of monetary gain versus anticipation of no monetary outcome for the A1 and A2 phases (A1Win and A2Win, respectively); 2) anticipation of monetary loss versus anticipation of no monetary outcome for the A1 and A2 phases (A1Loss and A2Loss, respectively); 3) win versus neutral outcome trials (OCWin); and 4) loss versus neutral outcome trials (OCLoss). To examine between-group differences, we compared activity in PG and CC groups during A1Win, A2Win, OCWin, A1Loss, A2Loss, and OCLoss in a series of *t* tests.

Given the small volume of the VS, together with evidence implicating this area in reward processing, the MIDT, and the pathophysiology

of PG, the VS was selected as an a priori region of interest (ROI). This ROI was defined and localized based on reward-processing findings of Breiter *et al.* (34). Activity from a spherical ROI of 3 mm radius (123 structural voxels $1 \times 1 \times 1$ mm) was extracted for each individual to examine the mean blood oxygen level-dependent percent signal change from baseline.

Then, activity during the anticipatory phases was examined between experimental groups using a one-way analysis of variance (ANOVA) in SPSS, version 17.0 (SPSS, Inc., Chicago, Illinois). The relationship between impulsivity and activity in the VS ROI during win and loss anticipation (win cues > neutral cues; loss cues > neutral cues) during A1 and A2 was examined using Pearson correlations.

Results

In-Scanner Behavior

Multiple one-way ANOVAs examining behavioral responses in scanner showed no significant between-groups differences in earnings, reaction times, or hit rates on the different incentive conditions (all $p > .05$; see Supplement 1).

Group Differences

A1Win. Between-group contrasts of neural activity during the A1Win phase revealed significantly decreased activity in PG relative to CC in the medial prefrontal cortex (mPFC) extending through the vmPFC and anterior cingulate into the left VS (Table 2, Figure 2A) and another cluster in the left inferior frontal gyrus. Conversely, activity in the medial precuneus was relatively increased in the PG group relative to the CC.

A1Loss. Similar between-group differences were observed during the A1Loss phase, associated with the prospect of losing money. Compared with the CC group, the PG group exhibited decreased activity in the left mPFC, extending ventrally into the anterior cingulate, as well as in the left inferior frontal gyrus, extend-

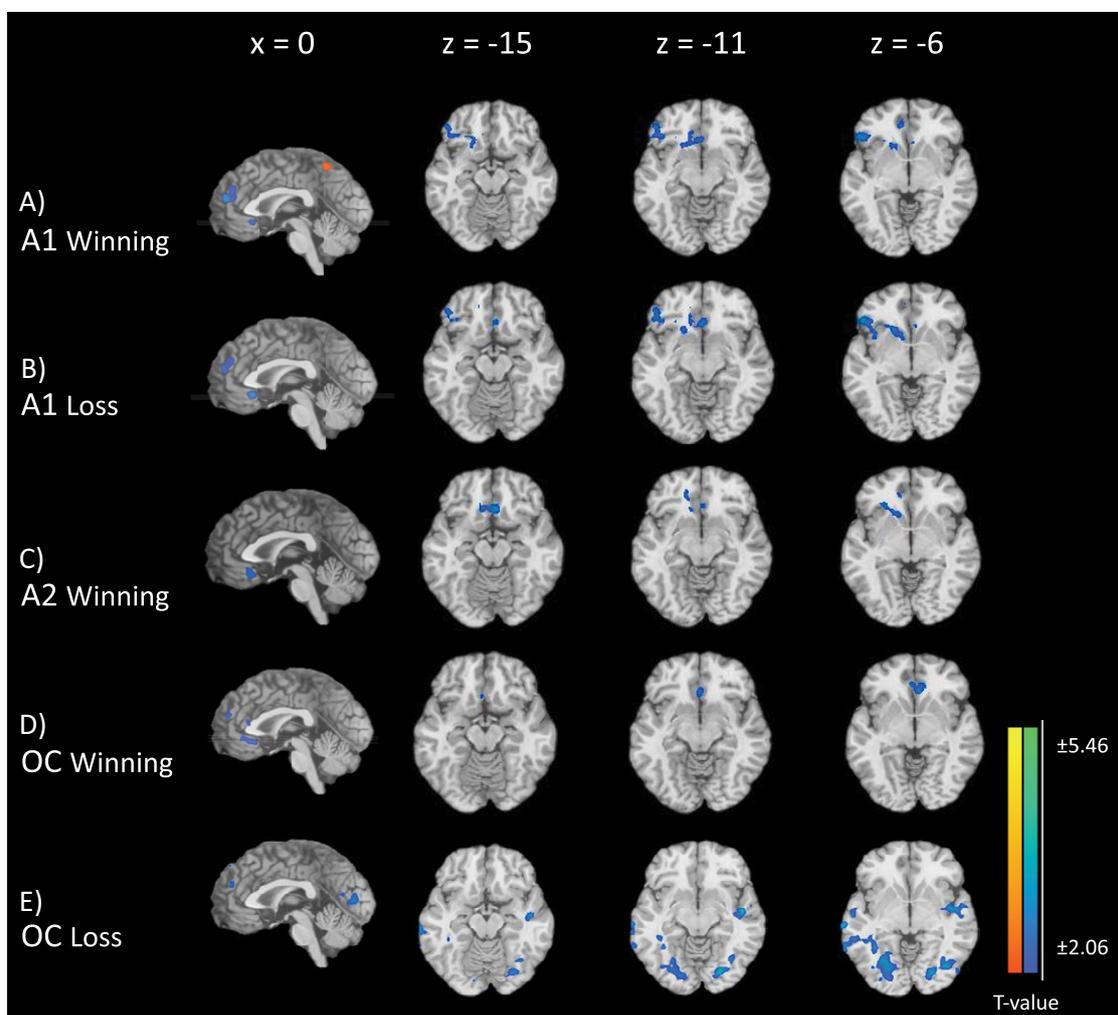


Figure 2. Group differences on the Monetary Incentive Delay Task in ventral frontostriatal areas: pathological gambling (PG) versus control comparison. Brain activation maps demonstrate differences in the PG group contrasted with the control comparison group during the (A) prospect of reward (A1) winning phase, associated with the prospect of monetary wins. Maps depict significant differences in the ventromedial prefrontal cortex (vmPFC), medial prefrontal cortex (mPFC) and precuneus ($x = 0$), ventral and lateral prefrontal cortex (PFC) ($z = -15, -11, -6$), and ventral striatum ($z = -11, -6$). (B) A1 losing phase, associated with the prospect of monetary losses. Maps depict significant differences in the vmPFC and mPFC ($x = 0$), ventral and lateral PFC ($z = -15, -11, -6$), ventral striatum ($z = -11, -6$), and left insula ($z = -6$). (C) A2 winning phase, associated with the anticipation of winning money. Maps depict significant differences in the vmPFC ($x = 0$; $z = -15, -11, -6$) and ventral striatum ($z = -11, -6$). (D) Outcome (OC) winning phase, associated with the receipt of a monetary reward. Maps depict significant differences in the mPFC and vmPFC ($x = 0$), vmPFC ($z = -15, -11, -6$), and ventral striatum ($z = -11, -6$). (E) OC losing phase, associated with the receipt of a monetary loss. Maps depict significant differences in the middle PFC and the middle occipital gyrus ($x = 0$, $z = -15, -11$), superior temporal gyrus ($z = -15, -11, -6$), middle temporal gyrus ($z = -11, -6$), and insula ($z = -11, -6$). All contrast maps are thresholded at an uncorrected level of $p < .05$ two-tailed and familywise error-corrected at $p < .05$ with a cluster threshold of 91. Blue color demonstrates areas where PG subjects show relatively less activation and red color indicates areas where PG subjects show relatively greater activation. For axial slices, the right side of the brain is on the right.

ing to the insula (Table 2). This pattern was also apparent in the left VS, extending to the vmPFC (Figure 2B).

A2Win. During A2Win, between-group differences involved the left vmPFC extending to the VS (Table 2, Figure 2C). This difference involved relatively decreased activity in the PG group.

A2Loss. No significant between-group differences were observed during A2Loss.

OCWin. During OCWin, decreased activity in the PG group was observed in the right vmPFC extending dorsally through the anterior cingulate and medially to the mPFC (Figure 2D). Another between-group difference involved the left posterior cingulate extending ventrally to the hippocampal gyrus (Table 2).

OCLoss. Loss versus neutral outcome trials were characterized by decreased activation in the PG group in multiple regions (Table

2, Figure 2, Figure S2 in Supplement 1). These included the right superior temporal gyrus extending into the insula, right occipital gyrus extending bilaterally into the lingual gyrus, cuneus and posterior cingulate, right superior parietal lobule, and left precentral gyrus and within a large cluster, in the left middle temporal gyrus extending into superior temporal and insular areas. Greater decreases in activity in the PG group were observed in the left superior and middle frontal gyri and bilateral mPFC.

ROI Analyses

Multiple one-way ANOVAs examining between-group differences in right VS activity revealed a significant difference during A1Loss [$F(1,26) = 4.91, p < .05$], A2Win [$F(1,26) = 4.72, p < .05$], and A2Loss [$F(1,26) = 5.12, p < .05$]. Between-group differences were

observed in the left VS during A2Loss [$F(1,26) = 4.57, p < .05$] and OCLoss [$F(1,26) = 4.35, p < .05$]. Inspection of ANOVAs revealed for all differences relatively decreased activation in the PG group.

Correlations Between Impulsivity and Reward Anticipation

Barratt Impulsivity Scale version 11 total and subscale scores are listed in Table 1. To test our hypotheses regarding VS activity and impulsivity, based on prior findings in alcohol dependence, Pearson correlations were calculated between ROI activity during the anticipatory phases and total and subscale scores on the BIS-11. During A2Win in the PG group, left VS activation correlated inversely with BIS-11 motor subscale scores ($r = -.55, p < .05$) and right VS activation correlated inversely with BIS-11 total ($r = -.63, p < .05$) and attention subscale ($r = -.76, p < 0.01$) scores during the A2Loss phase. There were no other significant correlations between the VS and BIS-11 scores in any other anticipatory phase for either the PG or CC groups (see Table S2 and Figure S1 in Supplement 1).

Discussion

Consistent with our hypotheses, PG as compared with CC participants showed diminished VS activation during reward anticipation, diminished vmPFC activation during reward outcome, and diminished insula activation during loss outcome. However, these patterns extended to wins and losses, were less phase-specific than hypothesized, and involved additional brain regions. As hypothesized, VS activity during the A2Win phase inversely correlated with impulsivity measures in the PG group. The biological and clinical implications are discussed below with respect to the relevant brain areas.

Between-Group Differences in vmPFC Activation

Pathological gambling participants demonstrated relatively decreased activity in overlapping vmPFC areas during the initial (prospect) anticipatory phase corresponding with the impending possibility of winning (A1Win) or losing (A1Loss) money, as well as during the second anticipation phase corresponding with the possibility of winning (A2Win; Figure 2A–C). Similar between-group differences were observed across winning and loss trials in the A1 phase involving overlapping areas of the mPFC (including vmPFC), VS, and left inferior frontal gyrus. These results provide evidence for significantly reduced recruitment of brain areas implicated in coding reward values, reward anticipation, and impulse control (11, 12, 29, 35–37) in PG relative to CC groups. Decreased activity in PG during anticipatory phases suggests alterations in the ability to signal and integrate the short-term value of an incentive cue. These findings have significant implications, as value integration can influence choice; indeed, in healthy populations, vmPFC recruitment during affective judgment is associated with adaptive decision making (38, 39). Therefore, reduced vmPFC recruitment in PG may contribute to less adaptive money-related decision making.

The vmPFC has been ascribed a role in integrating and updating information of executive processes from dorsolateral prefrontal cortex areas with affective information from insular and cingulate regions, thereby registering stimulus contingencies that can be used to forecast future consequences (35, 40). In the MIDT, increased vmPFC, as well as posterior cingulate, activity when an expected reward is obtained supports roles for these areas in monitoring monetary outcomes (12). In the present study, decreased activity in the vmPFC and posterior cingulate during the outcome phase of a winning trial in the PG group suggests possible deficits in PG related to tracking reinforcement contingencies. Relatively diminished vmPFC activity in the PG group accompanying anticipation and receipt of wins and losses therefore suggests diminished

integration of incentive information that might be used to guide subsequent behavior. This result resonates with findings in PG of perseverative response styles, deficits in decision-making tasks dependent on vmPFC function (41–43), and diminished vmPFC activation in PG during simulated gambling (3), cognitive control (21), gambling stimuli exposure (2), and decision making (4). Together, results suggest that reduced vmPFC activity is an important neural feature of PG across a range of cognitive processes.

Between-Group Differences in VS Activation

The vmPFC connects directly to the VS, predominantly with the nucleus accumbens, a region heavily implicated in reward processing, particularly as related to changes in affective states and goal-directed behaviors (44–46). The findings of relatively diminished VS responses in PG participants during the anticipation and outcome phases are consistent with findings of reduced VS activity in PG individuals during a simulated gambling/guessing task (3).

Reduced VS activity was observed in all anticipatory phases (A1Win, A1Loss, A2Win, and A2Loss) (Figure 2A–C, Table 2). Anticipatory processing may involve aspects of prospect and related motivations, anticipation of working for winning or avoiding losing, motoric responses, and anticipation of potential reward/loss. In an effort to model these phases more accurately than in some prior studies, the current experimental design models both A1 and A2 anticipatory phases, with the latter period occurring following motoric response. The behavioral results show no between-group differences in response times or correct hits, suggesting that the group differences in VS activity in A2Win and A2Loss may reflect differences in anticipatory processing rather than motoric demands or performance.

Relatively reduced VS activity in PG during both winning and losing anticipatory phases suggests a hypoactive reward system in response to monetary incentives and potential difficulties in maintaining reward expectations. The VS also contributes to temporal difference learning during aversive processing, whereby deviations of expected outcomes are signaled through striatal activity (47). In the current study, reduced VS response during the losing outcome phase in the PG group may denote that this result was unexpected. Together with the decreased vmPFC activity, they further lend support to the idea of a hyporesponsive frontostriatal system as important to PG.

Between-Group Differences in Insula Activation

Relative to the CC group, PG participants demonstrated decreased anterior insula activity during the A1Loss phase (associated with the prospect of losing money) and during the loss outcome phase (OCLoss). In healthy populations, the representation of aversive value recruits the anterior insula, as does the processing of uncertainty and risky choices (48–50). This area contributes to loss prediction since activity here predicts switching from more to less risky choices during financial risk taking (23, 49). Individuals with insular damage demonstrate increased betting on a gambling task, characterized by higher wagers and failures to adjust betting behavior when probabilities of losing increase (51).

In the current study, relative diminished insula activity in the PG group during the prospect of losing money may relate to altered loss-prediction signaling in this population. In healthy individuals, heightened insular activity during loss anticipation on the MIDT can predict future loss avoidance learning, suggesting that a loss-prediction signal may represent an important marker of adaptive avoidance behavior (52). Increased insular activity, together with ventrolateral prefrontal cortical function, appears to signal changes in the context of varying rewards (53), consistent with insular con-

tributions to integrating homeostatic signals with prior experiences and promoting adaptive choices and decision making (24,25,54). Therefore, decreased insula activity in the PG group observed during the prospect of loss may indicate diminished anticipatory signaling of information related to predicting and monitoring losses and could result in failures to adjust betting behavior or avoid risks.

Altered interoceptive awareness through blunted insular activity, particularly during the processing of losses, may relate to clinically relevant behavioral and cognitive processes in PG, such as loss chasing and cognitive distortions involving inflated confidence or illusions of control (55,56). The findings from the present study support a role for altered insula activity in PG populations during loss processing and suggest neural mechanisms that may underlie poor risk estimation in PG. Relative to control participants, diminished insula activity has previously been noted in PG during initial exposure to gambling cues and in an overlapping area in cocaine-dependent individuals when viewing cocaine cues (6). Diminished insula activity also has clinical relevance, as activity here during a decision-making task predicts time to relapse in substance-dependent individuals (57). Altogether, the role for the insula in signaling aversive value has led to the proposal of this area as an important therapeutic target in both PG and substance dependence (54,58).

Brain Activation and Impulsivity

Consistent with findings in alcohol dependence, we observed an inverse relationship between VS activity and measures of impulsiveness in the PG group, with whole-brain analyses implicating a broader range of corticostriatal areas. Analogous to alcohol-dependent individuals, higher BIS-11 motor subscale scores inversely correlated with VS activity in the PG group during reward anticipation (8). However, in contrast to the alcohol-dependence study, we separately modeled prospect (A1) and anticipation of notification (A2) phases of processing and thus linked the impulsivity finding more specifically to the A2 phase of processing. Another MIDT study separately modeling A1 and A2 phases also found a negative correlation between VS activity and impulsivity during the A2 phase in individuals with a positive family history for alcoholism (18). Our results therefore lend additional support to distinct neural phases associated with the prospect and the anticipation of reward/loss and further demonstrate consistent similarities across at-risk and addicted populations in relationships between impulsivity and VS activity during reward anticipation.

The current study further observed inverse correlations during the A2Loss phase between VS activity and both the BIS-11 total scores and the BIS-11 attention subscale scores, indicating diminished VS-related responsiveness to anticipated loss in association with elevated impulsivity. Notably, all VS correlations occurred during the A2 (rather than the A1) phase, highlighting in PG a specific relationship between impulsivity and VS activity during the anticipation of notification (rather than prospect) phase of reward and loss processing. Evidence in nonaddicted individuals suggests not only that individual sensitivity to future reward magnitude is proportionally reflected in VS activation but also that increased impulsivity is additionally inversely related to this diminished VS response (11,59). Together, data suggest that reduced VS responsiveness during reward and loss processing in PG may be reflected in elevated impulsivity and may influence decision-making and/or reward-seeking behaviors related to PG.

Whole-brain correlations related impulsivity to other corticostriatal regions including the vmPFC and insula during anticipatory phases. Interestingly, impulsivity correlated negatively with anterior cingulate activity in both A2Win and A2Loss. As the anterior cingulate contributes to loss-chasing during gambling (26), the

finding suggests that impulsivity may influence excessive gambling through cingulate mechanisms related to reward and loss processing. Future research should further examine these relationships, as impulsivity has been related to clinically relevant aspects of PG and its treatment. In a randomized clinical trial of paroxetine, self-reported impulsivity correlated with problem gambling severity at treatment onset, and changes in impulsivity correlated with changes in problem gambling severity during treatment (60). In an open-label trial of memantine, PG differed from control participants at treatment onset but not at treatment end on a behavioral measure of motor impulsivity, the stop-signal task (61). Thus, impulsivity may represent an important treatment target for PG. Given the relationship between impulsivity and VS activation during reward and loss processing, drugs that influence ventral striatal function and have data supporting efficacy in PG (e.g., opioid antagonists like naltrexone and nalmefene and glutamatergic agents like n-acetyl cysteine [62–64]) may be exerting their influences through decreasing impulsivity and normalizing VS function. This hypothesis warrants direct examination, particularly given the broader range of corticostriatal associations with impulsivity in PG.

Strengths, Limitations, and Future Directions

Previous studies examining monetary reward processes in PG have not parsed specific phases of processing that may differentially contribute to PG and clinically relevant aspects thereof. The current fMRI study is the first in PG to investigate distinct phases of reward and loss processing relating to prospect, anticipation, and notification. Moreover, relative to research in substance dependence in which brain changes may be attributable to the effects of a drug, the use of a PG population provides complementary information.

While this study incorporated both men and women, it is nonetheless limited by a sample size that does not permit examination of gender-related differences. Another drawback is the slightly greater number of smokers in the PG sample and the inclusion in the PG group of people with past psychiatric illnesses. Given the frequencies of comorbid psychiatric conditions in PG, particularly smoking (65), the current sample is representative of the general PG population. However, future studies should examine directly the influences of specific co-occurring disorders.

Although the findings were less phase-specific than originally hypothesized, the brain areas in which differences were observed represent predominant projection areas of the mesocorticolimbic dopamine system, which is consistent with dopamine's role in reward processing (66,67). While fMRI cannot relate activity changes to specific neurotransmitters, recent conjoint fMRI and positron emission tomography studies identified increased dopaminergic activity in prefrontal cortical areas as individuals anticipate and receive monetary rewards (68). Therefore, our findings of diminished activity in corticostriatal-limbic areas may reflect differences in dopaminergic function, particularly as alterations in striatal dopamine functioning have been reported in positron emission tomography studies of both PG and substance dependence (69–72). Reward and error prediction signaling in the VS and orbitofrontal cortex are attenuated by alterations in dopamine transmission (73); consequently, this neurotransmitter's effect on neuronal processing may impact an individual's ability to attribute value to cues, anticipate events, and learn from negative feedback. Future direct investigation of the relationships between the neural correlates of reward and loss processing as they relate to dopamine and other neurotransmitter function in PG is needed.

Understanding how the brain appraises incentive value further represents a fundamental parameter for decision-making pro-

cesses. The idea that adaptive decision making is promoted through activation of somatic and visceral states previously associated with advantageous choices has spurred research into identifying the neural substrates of affective signaling (15,74,75). For example, the vmPFC and insula have been ascribed roles in representing somatic and visceral states, particularly as they relate to negative arousal, with increased activity during negative or uncertain incentives (15,75,76). In linking the current body state with previously experienced outcomes, these brain areas may provide anticipatory signals to guide risky decision making (24,25,54,75). However, as the MIDT does not investigate choice, future research examining choice with respect to reward processing in PG is needed. Given the correlations between VS activity and impulsivity in PG without significant between-group differences in self-reported impulsivity or task performance, future experiments could more closely examine this relationship (e.g., using larger samples and/or behavioral measures of impulsivity). To better understand interoceptive states associated with gambling, future studies should use integrative approaches, including subjective, physiological, neural, and behavioral measures, to gauge homeostatic changes in PG. Additionally, such measures should be examined with respect to treatment outcome and include both self-report and behavioral measures, as these may differentially relate to addictive behaviors and their treatment (20,77).

Conclusions

The current study compared neural responses in anticipation of monetary rewards and punishments using a modified MIDT that parses prospect, anticipation, and outcome phases. Although the findings were less phase-specific than originally hypothesized, our findings demonstrate that during prospect and anticipation phases involving potential wins and losses, individuals with PG exhibit hypoactivity in neurocircuitry coding for the incentive value of stimuli. Specifically, this group shows a similar pattern of diminished VS and vmPFC responding during both winning and losing phases. Consistent with studies of alcohol dependence, we observed an inverse association during reward anticipation between impulsivity and VS activity in PG. These data provide evidence for similar alterations in neurocircuitry mediating anticipatory processing in both PG and substance addictions and that impulsivity may be similarly involved in these relationships. Treatment development efforts for PG might target normalizing activity in mesocorticolimbic neurocircuitry as related to impulsive thoughts and behaviors.

Support was provided by the following grants: National Institutes of Health Grants R01-DA019039, P20-DA027844, P50-AA012870, R01-DA020908, R01-DA020709, R01-AA016599, RL1-AA017539, and K12-DA00167; the Veterans Integrated Service Network 1 Mental Illness Research, Education, and Clinical Center; and a Center of Excellence in Gambling Research Grant from the National Center for Responsible Gaming and its Institute for Research on Gambling Disorders. The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Responsible Gaming or the Institute for Research on Gambling Disorders or any of the other funding agencies.

We gratefully acknowledge Jennifer Bellegarde, Mike Bernabeo, Scott Bullock, Cameron DeLeone, Stephen Healy, Jessica Montoya, Naaila Panjwani, Monica Solorzano, Jocelyn Topf, and Katie VanBuskirk for their help with the project.

Dr. Potenza has received financial support or compensation for the following: consults for and is an advisor to Boehringer Ingelheim; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Ad-

ministration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Psyadon, Ortho-McNeil, Oy-Control/Biotie, and Glaxo-SmithKline Pharmaceuticals; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders, or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has given academic lectures in grand rounds, continuing medical education events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. All other authors report that they have no biomedical financial interests or potential conflicts of interest with respect to the content of this manuscript.

Supplementary material cited in this article is available online.

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