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Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence☆

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ABSTRACT

Background: Individuals with gambling or substance-use disorders exhibit similar functional alterations in reward circuitry suggestive of a shared underlying vulnerability in addictive disorders. Additional research into common and unique alterations in reward-processing in substance-related and non-substance-related addictions may identify neural factors that could be targeted in treatment development for these disorders.
Methods: To investigate contextual reward-processing in pathological gambling, a slot-machine fMRI task was performed by three groups (with pathological gambling, cocaine dependence and neither disorder; $N = 24$ each) to determine the extent to which two groups with addictions (non-substance-related and substance-related) showed similarities and differences with respect to each other and a non-addicted group during anticipatory periods and following the delivery of winning, losing and 'near-miss' outcomes.
Results: Individuals with pathological gambling or cocaine dependence compared to those with neither disorder exhibited exaggerated anticipatory activity in mesolimbic and ventrocortical regions, with pathological-gambling participants displaying greater positive possible-reward anticipation and cocaine-dependent participants displaying more negative certain-loss anticipation. Neither clinical sample exhibited medial frontal or striatal responses that were observed following near-miss outcomes in healthy comparison participants.
Conclusions: Alterations in anticipatory processing may be sensitive to the valence of rewards and content-disorder-specific. Common and unique findings in pathological gambling and cocaine dependence with respect to anticipatory reward and near-miss loss processing suggest shared and unique elements that might be targeted through behavioral or pharmacological interventions in the treatment of addictions.

1. Introduction

Individuals with gambling and substance-use disorders (SUDs) exhibit neurobiological similarities, particularly in reinforcement/reward/motivation circuitry (Leeman and Potenza, 2012; Potenza, 2008). Specifically, aberrant ventral striatal and ventrocortical function appear common across disorders and is consistent with models of addiction that encompass substance-related and non-substance-related behaviors (Potenza, 2013). However, the extent to which increased or blunted activation of reward circuitry is observed in pathological gambling (PG; gambling disorder in DSM-5) and SUDs has been debated, with data suggesting that context (e.g., gambling for PG or substances for SUDs) may determine whether increased or blunted activation is observed (Leyton and Vezina, 2013; Limbrick-Oldfield et al., 2013; van Holst et al., 2012b). Continued research into shared and unique alterations in

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reinforcement-related processes in PG and SUDs that consider such contexts may help identify neural factors that could be targeted in treatment development for these disorders (Insel et al., 2010; Potenza, in press; Potenza et al., 2011).

Electronic gambling machines (EGMs), popularly termed slot machines, are a prevalent form of gambling that some have argued is the most addictive form of gambling (Schüll, 2012), although this has been debated (Dowling et al., 2005). Specific features of EGMs have been cited as potentially addictive in that they may influence or interact with gambling-related cognitions and contribute to reinforcement learning and persistent gambling (Potenza, in press; Schüll, 2012). One such feature is the 'near-miss' phenomenon, a gambling-related experience that is typically encountered during EGM gambling. Defined as losing outcomes that are perceived as 'close' to being successful (Reid, 1986), near-miss outcomes occur when all but one of the reels display matching symbols (e.g., AAB). Although the monetary value of near-miss outcomes are equivalent to other losses, near-miss outcomes are associated with increased physiological arousal (Clark et al., 2012; Dixon et al., 2011), and in laboratory situations, can lengthen the duration of gambling sessions in both occasional and regular players (Côté et al., 2003; Dixon and Schreiber, 2004; Kassinove and Schare, 2001; MacLin et al., 2007). Models of how near-miss outcomes may encourage continued gambling suggest these events may promote erroneous gambling-related beliefs related to skill and illusions of control (Billieux et al., 2012; Clark et al., 2012) and activate appetitive mechanisms through activity in reward/reinforcement circuitry (Chase and Clark, 2010; Dixon et al., 2013).

Previous research in which occasional and at-risk gamblers participated in simulated slot-machine gambling has found that the delivery of near-miss outcomes relative to full-losses (e.g., slot-machine outcomes where no symbols match) is associated with increased activity within reward/reinforcement circuitry including the ventral striatum, insula, and midbrain (Chase and Clark, 2010; Clark et al., 2009). Similarly, individuals with problem gambling also exhibited increased activity in reward-related regions following the delivery of a near-miss (Habib and Dixon, 2010), suggesting near-miss outcomes may promote continued gambling through positive reinforcement (despite being monetary losses). However, in individuals with PG or SUDs, groups that have been found to exhibit altered patterns of neural activations during monetary reward/loss processing (Balodis et al., 2012; Goldstein et al., 2007; Jia et al., 2011; Peters et al., 2011; Reuter et al., 2005; Wrase et al., 2007), it is unclear if neural function underlying the processing of near-miss events will be similar or different across the groups with non-substance and substance addictions.

Previous fMRI investigations of near-miss experiences have focused upon differences between neural signals evoked by winning, losing and near-miss outcomes (Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010). However, reinforcement-related neural responses develop through conditioned learning of predictive stimuli, and this association is expressed during anticipatory states (Fiorillo et al., 2008; Montague et al., 1996; Roesch et al., 2010; Schultz et al., 1997). PG and SUDs are associated with differences in anticipatory reward-processing (Balodis et al., 2012; Choi et al., 2012; Jia et al., 2011; van Holst et al., 2012a; Wrase et al., 2007) and thus warrant investigation.

In the current experiment, fMRI was used to investigate neural activity associated with reward-anticipation and near-miss outcomes while individuals with PG, cocaine dependence (CD; cocaine-use disorder in DSM-5) and neither disorder performed a simulated 'three-wheel' slot-machine fMRI task. We examined between-group differences in whole-brain activity associated with two types of near-miss outcomes (non-sequential and sequential near-misses, see Section 2.2.) as compared to other losing events. We had competing hypotheses. Consistent

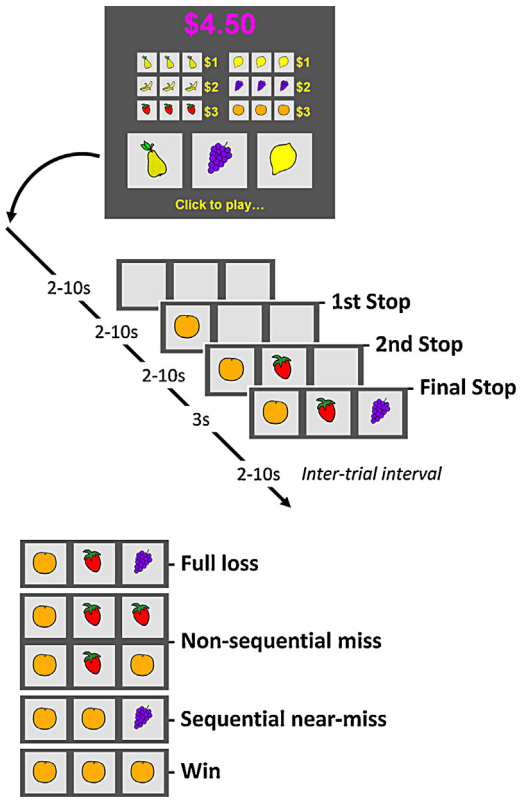

Fig. 1. Simulated slot-machine task design and example outcome types.

with models of gambling-related cue and reward hypersensitivity in PG (Leyton and Vezina, 2013; Limbrick-Oldfield et al., 2013; van Holst et al., 2012b), we hypothesized that individuals with PG would exhibit increased reward-anticipation and near-miss activity in striatal and ventrocortical circuitry as compared to CD and healthy comparison (HC) participants. Alternatively, if reward/reinforcement/motivation processes were shared across PG and CD, we had a competing hypothesis that both groups would demonstrate increased reward-anticipation and near-miss activity in striatal and ventrocortical circuitry as compared to HC participants.

2. Materials and methods

2.1. Participants

Participants included 24 individuals with PG, 24 with CD, and 24 HC individuals (Table 1) recruited from the local (New Haven, CT) community. All participants were assessed for DSM-IV diagnoses using semi-structured clinical interviews (SCID; (First et al., 2002)). Exclusion criteria included the presence or history of a psychotic disorder or general medical illness that would interfere with the ability to participate in screening, assessment or fMRI protocols. Urine toxicology screening for illicit substances was performed at the time of scanning. All study procedures were approved by the Yale Human Investigations Committee. Participants provided written informed consent.

2.2. Simulated slot-machine task

Participants performed a computer-simulated, three-reel slot-machine task designed for fMRI (Fig. 1). On each play, participants pushed a button after which all three 'reels' began randomly changing through six different fruit symbols every 200 ms to simulate spinning slot-machine reels. To maximize the expectancy and impact of the near-misses and other outcomes, the reels stopped in sequential order from left to right (Strickland and Grote, 1967). Colinearity of events was minimized by using durations of reel spins and inter-trial intervals that were pseudo-randomly presented between 2 and 10 s, with an average of 6 s, for an average total single play length of 18 s.

Outcomes were presented in one of four predetermined pseudorandom orders (balanced across groups), delivering approximately 17% (according to a variable ratio of 1:6) winning (e.g., AAA), sequential near-miss (e.g., AAB) and non-sequential

Table 1
Participant characteristics and behavioral performance.

Variable	HC	PG	CD	F/χ^2	P
Demographic characteristics					
N	24	24	24	–	–
Age, years (SD)	33.4 (10.5)	38.2 (10.9)	42.6 (5.5)	5.89[a]	0.004
Female, *N* (%)	11 (45.8)	9 (37.5)	8 (33.3)	0.82[a]	0.66
Estimated IQ, SILS (SD)	106.3 (10.2)	102.5 (13.6)	94.4 (9.7)	7.23[a]	0.001
Clinical characteristics					
Impulsivity, BIS (SD)	51.3 (8.1)	67.8 (11.6)	63.9 (12.1)	15.48[a]	<0.001
Depression, BDI (SD)	1.9 (4.0)	11.3 (8.2)	5.8 (6.0)	13.33[a]	<0.001
Tobacco use, FTND (SD)	0 (0)	1.7 (2.9)	3.2 (3.5)	9.12[a]	<0.001
Alcohol use, AUDIT (SD)	1.9 (1.6)	6.8 (7.9)	4.5 (6.7)	3.91[a]	0.025
Problem-gambling severity, SOGS (SD)	0.3 (0.4)	13.1 (3.8)	2.9 (4.7)	88.83[a]	<0.001
Gambling cognitions, GRCS (SD)	31.3 (12.8)	91.9 (23.4)	49.3 (32.1)	39.89[a]	<0.001
Disorder chronicity, years (SD)	–	15.9 (11.8)	12.0 (9.2)	1.68[b]	0.20
Lifetime major depression, *N* (%)	–	4 (16.7)	2 (8.3)	0.76[b]	0.38
Problematic EGM gambling, *N* (%)	–	4 (16.7)	–	–	–
Slot-machine performance					
Average initiation time, ms (SD)	668 (188)	629 (235)	623 (205)	0.33[a]	0.72
Post-reinforcement pause, ms (SD)	224 (428)	134 (153)	158 (273)	0.55[a]	0.58

Abbreviations: HC, Healthy comparison, PG, pathological gambling; CD, cocaine dependence; SILS, Shipley Institute of Living Scale; BIS, Barrat Impulsivity Scale; BDI, Beck Depression Inventory; FTND, Fagerstrom Test of Nicotine Dependence; AUDIT; Alcohol Use Disorder Identification Test; SOGS, South Oaks Gambling Screen; GRCS, Gambling-related Cognitions Scale; EGM, electronic gaming machine.

[a] df = 2,69.

[b] df = 1,46.

miss (e.g., ABA, ABB) outcomes. Full-loss outcomes (e.g., ABC) were delivered on the remaining 50% (variable ratio of 1:2). The slot-machine task was performed in the scanner in two consecutive acquisitions of 30 plays each. Participants were given an endowment of $5 to begin each session, paid $0.10 per gamble for opportunities to win $1, $2 or $3 prizes, and were paid their total winnings for both sessions (ranging between $23 and $25) in addition to a fixed compensation for participation.

The slot-machine task afforded a behavioral measure of reaction time to initiate the next gamble following different outcomes, measured from the onset of the prompt to begin to the subsequent response. Outlying initiation times were identified by outcome-type using shifting z-score criteria as previously described (Dixon et al., 2013), removing 3.4% of the total data prior to calculating participant averages. Standard repeated-measures ANOVAs were utilized to examine differences in initiation times and corrected for sphericity violations using Greenhouse–Geisser estimates.

2.3. fMRI acquisition, image processing and statistics

Due to an equipment upgrade, image acquisition was performed on two Siemens Trio 3T systems (Siemens AG, Erlangen, Germany), with approximately half of each participant group scanned on each magnet. Identical acquisition procedures and sequences were employed on both magnets. Functional images were collected using an echo-planar image gradient echo pulse sequence (repetition time/echo time: 1500/27 ms, flip angle 60°, field of view: 22 × 22 cm, 64 × 64 matrix, 3.4 × 3.4 mm in-plane resolution, 5 mm effective slice thickness, 25 slices). Each functional run included an initial rest period of 9 s that was removed prior to image processing.

Spatial processing was performed using SPM8 (Wellcome Functional Imaging Laboratory, London, UK). Functional runs were realigned individually and examined for head motion in excess of one acquisition voxel. Realigned image volumes for each session were used to construct a mean functional image volume, which was then used for spatial normalization into Montreal Neurological Institute (MNI) standardized space. The normalization parameters for each participant were applied to the corresponding functional image volumes using an automated spatial transformation resulting in an isometric voxel size of 3 × 3 × 3 mm. Normalized images were then smoothed with a 6 mm full-width-at-half-maximum Gaussian filter. Of a total of 84 participants completing the slot-machine-task scanning, 12 participants were excluded for excess motion.

Functional data analysis was conducted using general linear modeling. First-level (participant) models included 13 task-related regressors. These included event-related regressors (i.e., duration = 0 s) for prompts to initiate gambles, responses, first-reel stops, second-reel stops with matching or unmatched symbols, and the four outcome arrangements (described above) delivered at the third-reel stop. In addition, regressors were also included for the intervals between reel-stops (i.e., the 2–10 s durations before and after the first-reel stop, and following the second-reel stop while the final reel was spinning with matched or unmatched symbols displayed on the first two reels). Potential-reward value was also included as a parametric regressor for applicable reel-stop events and spin epochs. Finally, the six realignment parameters resulting from image processing were included in the model. Contrast images between events of interest were calculated for each participant and entered into second-level random effects models to investigate differences between groups.

Second-level analyses were performed for each contrast of interest using 3-way (group) factorial designs, which included covariates to control for potential influences of magnet and demographic characteristics of gender, age and IQ (Shipley Institute of Living Scale, SILS; Zachary and Shipley, 1986). Average activity related to task events across all participants was examined using a cluster-level family-wise error (FWE) correction threshold (Ward, 2011) of $P_{FWE} < 0.05$ (cluster extent greater than 125 contiguous voxels) applied to voxel-level threshold of $P < 0.01$. In examination of main effects of group, few clusters survived correction at this voxel-level threshold, and thus a similar cluster-level threshold of $P_{FWE} < 0.05$ (cluster extent greater than 189 contiguous voxels) was applied to resulting whole-brain results of group differences at reduced voxel-level $P < 0.02$. In addition, a cluster-level uncorrected threshold of $P < 0.05$ (cluster extent greater than 44 contiguous voxels) was applied at the same voxel-level $P < 0.02$ results to explore less volumetrically robust group differences in regional activity.

Average BOLD responses in identified clusters were extracted for each participant to investigate pairwise group differences and within-group activity. The extracted average signals for each cluster were also re-tested for group differences using univariate analyses with additional covariates for alcohol (Alcohol Use Disorder Identification Test, AUDIT; Bush et al., 1998) and tobacco use (Fagerstrom Test of Nicotine Dependence, FTND; Heatherton et al., 1991), as well as after excluding the four individuals with CD who reported a prior history of PG. All significant group differences survived these additional tests at $P < 0.05$. Linear regression analyses were employed to explore relationships between BOLD responses and clinical measures of impulsivity (Barratt Impulsivity Scale, BIS; (Patton et al., 1995)), depression (Beck Depression Inventory, BDI; Beck et al., 1996); problem-gambling severity (South Oaks Gambling Screen, SOGS; Lesieur and Blume, 1987), gambling-related cognitions (Gambling-Related Cognitions Scale, GRCS; Raylu and Oei, 2004) and disease chronicity; however, no associations survived multiple-comparison corrections.

3. Results

3.1. Participant characteristics and behavioral performance

Participant characteristics are summarized in Table 1. Briefly, PG and HC participants did not differ in age or estimated IQ ($t_{1,46}$'s < 1.6, P's > 0.10). CD participants were older than HC participants ($t_{1,46} = 3.80$, $P < 0.001$) and of a lower average estimated IQ than both PG ($t_{1,46} = 2.37$, $P = 0.022$) and HC ($t_{1,46} = 4.24$, $P < 0.001$) groups.

PG participants reported greater lifetime problem-gambling severity than CD ($t_{1,46} = 8.24$, $P < 0.001$) and HC ($t_{1,46} = 16.40$, $P < 0.001$) participants (Table 1). PG participants indicated a variety of regular gambling activities (e.g., lotteries, casino games, sports betting), with regular engagement in an average of 2.7 (SD = 1.9)

different gambling activities (Supplemental Table S1[2]). Four PG participants reported problematic slot-machine gambling, with three of these individuals also reporting participation in multiple gambling activities. CD participants reported greater lifetime problem-gambling severity relative to HC participants ($t_{1,46} = 2.69$, $P = 0.01$). Four CD participants reported a lifetime (non-current) history of probable PG (SOGS = 5 or higher). HC participants' problem-gambling severity scores (SOGS ranging from 0 to 1) indicate minimal gambling severity and are consistent with scores in the general population (Stinchfield, 2002). PG and CD participants did not differ on duration of disorder, tobacco use, alcohol use ($t_{1,46}$'s < 1.7, P's > 0.1) or frequencies of co-occurring lifetime major depression (Table 1).

Average times to initiate the slot-machine did not differ between groups (Table 1). Across participants, initiation times differed by preceding outcome ($F_{1.7,120.0} = 18.27$, $P < 0.001$; Supplemental Fig. S1[3]), with initiation times following winning outcomes being greater than those following all other outcomes ($F_{1,69}$'s > 17.0, $P < 0.001$). This post-reinforcement pause effect has previously been observed during slot-machine gambling (Dixon et al., 2013;Table 1). Initiation times following non-sequential misses were faster than full-loss outcomes across participants ($F_{1,69} = 4.17$, $P = 0.04$). Initiation times following sequential misses were no different than non-sequential misses or full losses across participants ($F_{1,69}$'s < 0.7, P's >0.4). There were no group differences in extended or shortened initiation times ($F_{2,69}$'s < 0.5, P's > 0.6).

3.2. Reward-receipt

Although primary hypotheses focused on anticipatory and near-miss processing, we examined activity associated with winning outcomes to verify task validity in evoking expected reward-related responses, and explored group differences to identify altered regional activity associated with processing of rewards. Reward-receipt processing was examined following the delivery of winning outcomes relative to unmodeled brain activity (e.g., AAA vs. implicit baseline). All groups exhibited regional activations in well-established reward-receipt processing regions (Liu et al., 2011) including the ventral striatum, midbrain, amygdala, insula, and ventromedial prefrontal, cingulate, and parietal cortices (Fig. 2; Table 2). There was no main effect of group in regional BOLD signals in response to winning outcomes, either at whole-brain corrected or uncorrected cluster thresholds.

3.3. Reward-anticipation

Group differences in reward-anticipation were examined by comparing activity during the period of the third-reel spinning while either matched or unmatched symbols were displayed on the first two reels (e.g., AA? vs. AB?). That is, activity associated with anticipating potential rewarding outcomes was compared to activity associated with anticipating certain losing outcomes. Across all groups, anticipation of possible reward was associated with increased activity in the striatum, insula, midbrain, anterior cingulate, middle and superior frontal cortex and inferior parietal cortex (Fig. 3a; Table 2). There was a main effect of group in several regions (Fig. 3b; Table 3), notably the right ventral striatum, midbrain, and right insula. Further investigation of the individual anticipatory periods revealed a group-by-anticipation interaction in these regions including the ventral striatum ($F_{2,64} = 9.62$, $P < 0.001$), with PG relative to HC participants displaying increased potential-reward anticipation, and CD relative to PG and HC participants displaying reduced certain-loss anticipation (Fig. 3c). Similar patterns of increased possible-reward-anticipation in PG, and decreased loss-anticipation in CD, were present in midbrain, insular and cortical regions.

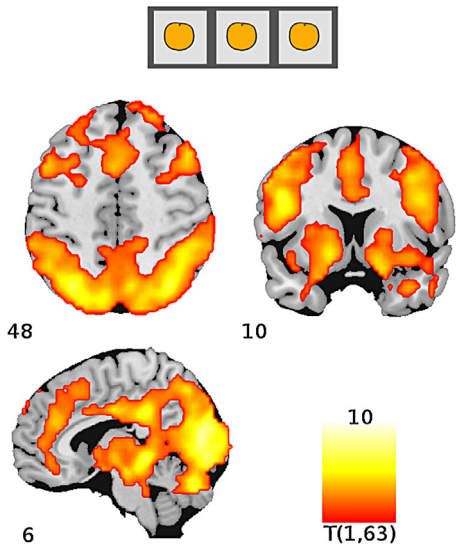

Fig. 2. Reward-receipt processing. Whole-brain, cluster corrected ($P_{FWE} < 0.05$) responses to slot-machine winning outcomes (e.g., AAA) across participants.

3.4. Near-miss loss-processing

Group differences in near-miss processing were examined utilizing two contrasts. First, a comparison between non-sequential miss and full-loss outcomes (e.g., ABA/ABB vs. ABC) was performed to examine differences in activity following the delivery of outcomes in gambles that had already been lost on the second reel-stop. By controlling for any differences in gamble expectations (i.e., both outcomes deliver certain losses), this contrast isolates brain activity associated with non-sequential misses being encoded as 'closer' to a winning outcome. Across all participants non-sequential miss outcome were associated with increased responses in occipital regions as well as the posterior cingulate cortex and inferior and superior parietal regions (Fig. 4a; Table 2). There was a main effect of group in non-sequential miss-related activity in the dorsomedial and ventromedial frontal cortex at uncorrected thresholds (Fig. 4b; Table 3). Investigation of the certain losing outcomes revealed a group-by-anticipation interaction in these regions including the ventromedial prefrontal cortex ($F_{2,64} = 8.72$, $P < 0.001$). HC relative to PG participants exhibited greater negative responses following non-sequential misses, while CD relative to HC participants displayed greater negative responses following full-loss outcomes (Fig. 4c). Notably, individuals with PG did not exhibit differential responses to non-sequential misses relative to full-losses in medial frontal regions.

Second, differences in near-miss processing were examined by comparing activity following sequential miss outcomes to activity following unmatched second-reel stops (i.e., AAB vs. AB). This contrast controls for the notification of a loss, and thus isolates activity associated with whether losing on the third-reel is encoded as 'closer' to a winning outcome than a loss delivered on the second-reel. Across participants, sequential miss outcomes were associated with increased activity in occipital regions extending into the posterior cingulate (Fig. 5a; Table 2). A main effect of group was identified in several regions at whole-brain-uncorrected

[2] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

Table 2
Average regional brain activity associated with slot-machine task events.

Region/Gyrus	BA	k	x	y	x	T
Reward-receipt						
Winning outcome vs. implicit baseline						
R Occipital	18, 19	23,045	27	−70	−11	10.10
Sub-clusters:[a]						
R/L Cingulate	23, 24, 31		3	−34	31	6.96
L Inferior/middle frontal	8, 9, 45, 46		−48	11	28	6.51
R Inferior/middle frontal	8, 9, 10, 45, 46		45	14	28	6.56
L Inferior frontal, insula	47		−30	23	−17	6.58
L Amygdala, putamen, parahippocampal			−21	−1	−26	6.19
R Amygdala, putamen, parahippocampal			15	5	−17	5.29
R Anterior cingulate	9, 32		9	35	22	4.91
L/R Superior/medial frontal	6, 32		−3	11	49	4.63
Reward anticipation						
Final-reel spin, matched vs. unmatched						
R Occipital, inferior temporal	18, 19, 37, 40	4442	42	−82	4	6.94
Sub-clusters:[a]						
L Occipital, inferior temporal	18, 19, 37		−42	−76	−5	6.07
R Occipital, inferior/superior parietal	7, 40		30	−76	28	7.93
R Cerebellum			18	−76	−26	5.21
L Inferior/middle frontal, insula	6, 9, 13, 44, 45, 46, 47	8577	39	26	10	6.91
Sub-clusters:[a]						
L Inferior/middle frontal, insula	6, 9, 13, 44, 45, 47		−30	29	1	6.62
L/R Thalamus, midbrain, caudate, putamen			6	−19	1	5.92
L/R Superior frontal	6, 8, 9		0	5	64	5.07
L Inferior parietal	7, 40		−54	−43	28	3.98
L/R Occipital, posterior cingulate	17, 18, 19, 23, 30, 31	1263	−9	−79	−2	−4.45
Near-miss processing						
Non-sequential miss vs. full-loss						
L Parietal, L/R occipital, posterior cingulate	7, 17, 18, 19, 23, 30, 31, 40	2674	−39	−43	34	4.67
R Inferior/superior parietal	7, 19, 40	430	51	−43	58	3.81
Sequential-miss vs. second-reel matched stop						
R Occipital, cerebellum, posterior cingulate	18, 19, 30, 31	988	30	−79	−8	4.05
L Occipital	17, 18, 19	309	−9	−100	7	4.52

[a] Sub-clusters are reported to detail regional constitution of large contiguous clusters. Sub-clusters were defined as localized activity that survive as individual clusters at more stringent voxel-level thresholds.

thresholds, including right ventral striatum, right insula, right inferior frontal gyrus and right parietal regions (Fig. 5b; Table 3). HC relative to PG and CD participants exhibited increased activity in response to sequential-miss outcomes across identified clusters including the ventral striatum (Fig. 5c). Individuals with PG and CD did not display differential signaling following sequential-miss outcomes as compared to second-reel matched stops.

4. Discussion

The present study investigated shared and unique alterations in reward/loss processing in PG and CD by examining regional brain activity during reward anticipation and following near-miss outcomes during performance of a simulated slot-machine task. Individuals with PG relative to CD and HC participants exhibited

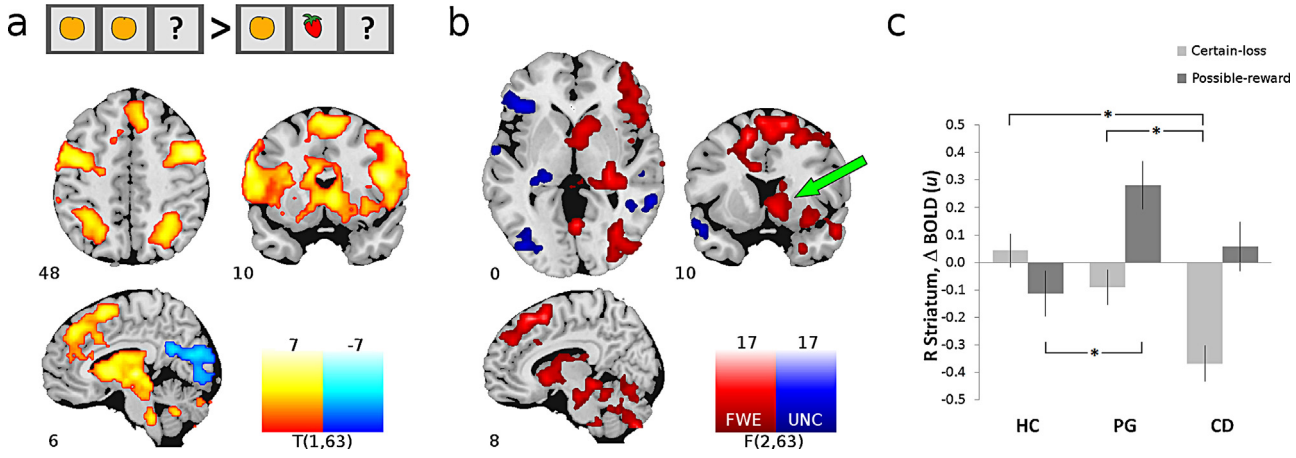

Fig. 3. Anticipatory processing. Average anticipatory whole-brain response across all participants (a) at cluster-corrected ($P_{FWE} < 0.05$) threshold while watching final reels spin while the first two reels display matching symbols (e.g., AA?; indicating potential win anticipation) as compared to unmatched symbols (e.g., AB?; indicating certain-loss anticipation). Group differences in anticipatory activity (b) at whole-brain cluster-corrected (red) and uncorrected (blue) thresholds. Regional BOLD signal differences between groups in the right striatum during reward-anticipation are shown in (c). All error bars indicate standard error. Abbreviations: HC, healthy comparison; PG, pathological-gambling; CD, cocaine-dependent; u, arbitrary units. * $P < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Regional group differences in brain activity associated with slot-machine events.

Region/Gyrus	BA	k	x	y	x	F
Reward-receipt						
Winning outcome vs. implicit baseline						
No significant clusters						
Reward anticipation						
Final-reel spin, matched vs. unmatched						
L/R Cerebellum		683	12	−73	−47	17.25
L/R Superior/medial/middle frontal, cingulate	6, 8, 9, 32	1392	6	26	55	15.51
L/R Midbrain, R hippocampus, putamen, occipital	19	1025[a]	27	−22	4	13.54
L Cerebellum		54	−54	−52	−38	11.47
R Inferior frontal, insula, superior temporal	13, 21, 38, 45, 47	751[a]	36	29	−11	11.47
R Middle/superior temporal	22	98	45	−49	7	11.07
L Hippocampus		60	−33	−25	−14	9.58
R Superior/inferior r parietal	7, 40	198[a]	21	−46	43	9.45
R Caudate	40	325[a]	9	11	−2	9.12
L Inferior frontal	47	98	−42	29	1	8.59
L Precuneus	7	54	−18	−58	46	8.31
L Inferior parietal	40	47	−60	−46	37	8.30
L Inferior parietal	40	88	−30	−43	40	8.18
L Occipital	19	152	−39	−79	7	7.77
L Superior/middle temporal,	21, 38	127	−63	−7	4	7.73
L Cerebellum		81	−27	−55	−23	7.50
R Middle temporal	21	69	60	−22	−11	7.46
Near-miss processing						
Non-sequential miss vs. full-loss						
L/R Medial frontal, anterior cingulate	10, 32	89	−15	38	−5	10.46
L/R Medial/superior frontal	8, 9, 10	172	−9	47	28	7.72
R Inferior temporal	20	50	48	−10	−29	7.48
Sequential-miss vs. second-reel matched stop						
L Occipital	19	123	−36	−79	4	11.06
R Occipital, cerbellum		63	21	−85	−11	10.74
R Cerebellem	19	63	15	−58	−47	9.28
R Inferior parietal	40	111	51	−49	55	9.07
R Middle frontal	11	55	39	44	−14	9.04
R Middle frontal	46	81	51	41	22	8.77
R Superior parietal	7	76	18	−73	61	6.95
R Putamen		68	24	8	−11	6.59
R Inferior frontal, insula	47	55	48	23	−2	6.42

[a] Survives whole-brain cluster-correction $P_{FWE} < 0.05$.

heightened activity during potential-reward anticipation in regions including the ventral striatum, insula, and medial prefrontal cortex, consistent with models in which gambling contexts elicit in PG enhanced activation of reward circuitry (Leyton and Vezina, 2013; Limbrick-Oldfield et al., 2013; van Holst et al., 2012b). Individuals with CD relative to PG and HC participants displayed greater deactivation during certain-loss anticipation in reward-related regions. Group differences in near-miss responses were observed in striatal and ventrocortical regions, with PG and CD groups showing similarly blunted activation of the ventral striatum to sequential miss outcomes relative to HC participants. The findings of common differences in processing of loss-related events in PG and

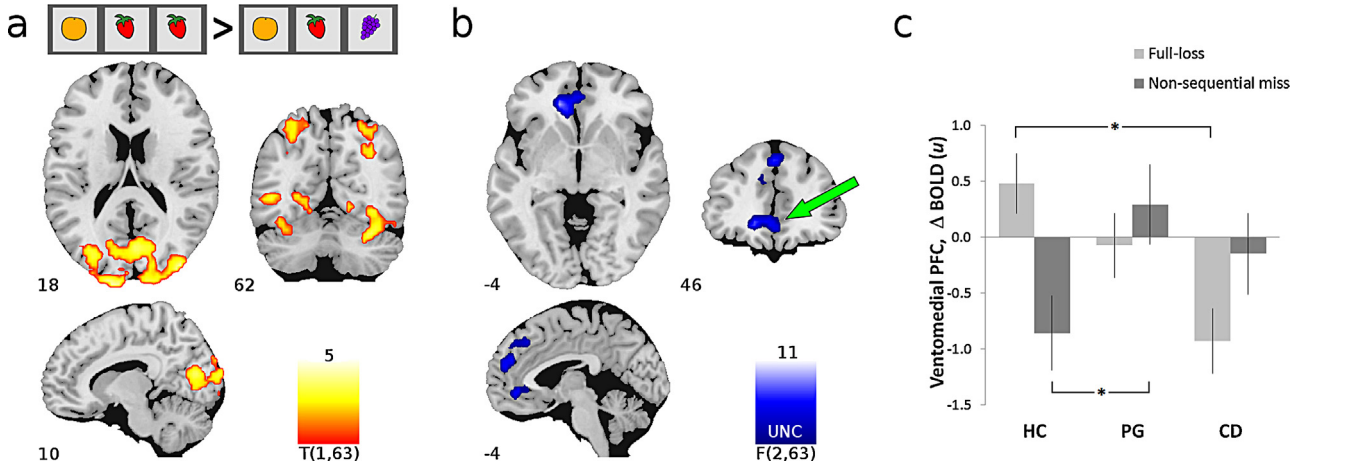

Fig. 4. Non-sequential near-miss processing. Average whole-brain response in response to non-sequential misses (e.g., ABB/ABA) as compared to full-loss outcomes (e.g., ABC) across all participants (a) at cluster-corrected ($P_{FWE} < 0.05$) threshold. Group differences in spatial near-miss activity in these certain-loss outcomes (b) did not survive cluster-correction thresholds, but are displayed at uncorrected (blue) cluster threshold of $P < 0.05$. Average regional BOLD signal differences between groups in the ventromedial prefrontal cortex (PFC) are shown in (c). All error bars indicate standard error. Abbreviations: HC, healthy comparison; PG, pathological-gambling; CD, cocaine-dependent; u, arbitrary units. * $P < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

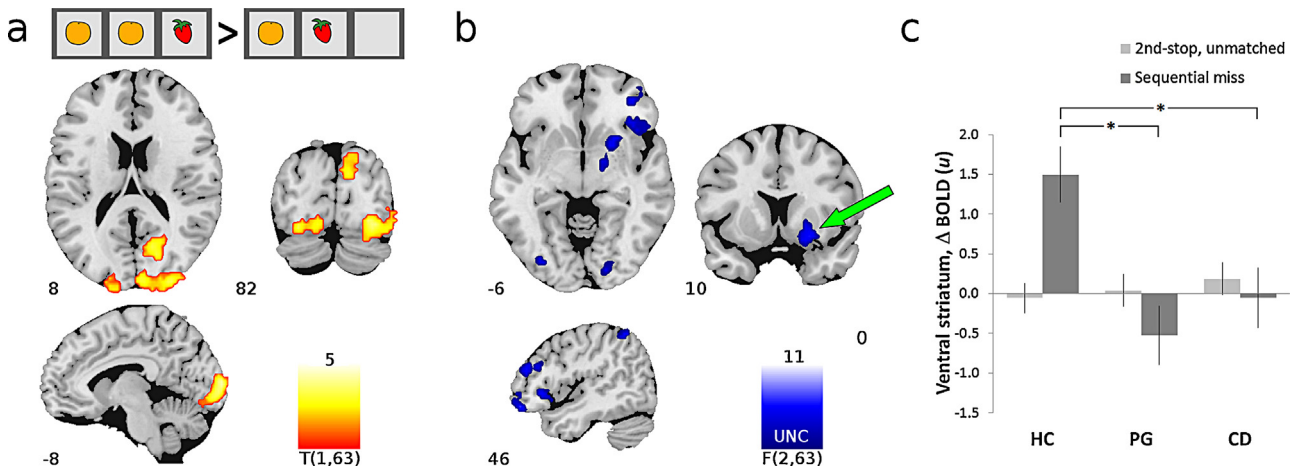

Fig. 5. Sequential near-miss processing. Average whole-brain response in response to sequential misses (e.g., AAB) as compared to second-reel unmatched (e.g., AB), losing events across all participants (a) at cluster-corrected ($P_{FWE} < 0.05$) threshold. Group differences in temporal near-miss activity in these notification of loss events (b) did not survive cluster-correction thresholds, but are displayed at uncorrected (blue) cluster threshold of $P < 0.05$. Regional BOLD signal differences between groups in the right ventral striatum are displayed in (c). All error bars indicate standard error. Abbreviations: HC, healthy comparison; PG, pathological-gambling; CD, cocaine-dependent; u, arbitrary units. * $P < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CD suggest that the function of brain circuitry (including the ventral striatum) underlying specific aspects of reward/loss processing may be shared across substance and non-substance addictions. The extent to which such factors may relate to addiction vulnerability, progression and recovery warrants additional investigation.

4.1. Anticipatory reward and loss processing

The most robust findings in the present study were observed prior to the delivery of slot-machine outcomes, with the PG and CD participants displaying alterations in anticipatory signals, particularly in the ventral striatum, insula, medial and inferior frontal cortex as compared to HC participants. Both clinical samples exhibited patterns of activity in reinforcement circuitry that were greater in anticipation of a possible-reward as compared to a certain-loss. However, consistent with hypotheses and previous research (van Holst et al., 2012a), individuals with PG exhibited increased striatal activity during anticipation of a possible winning outcome. By comparison, individuals with CD exhibited greater striatal deactivation during anticipation of certain losing outcomes. These findings suggest that while both substance-related and non-substance-related addictions are characterized by dysregulation in anticipatory-reward-processing mechanisms, there exist disorder-specific aspects relating to valence (rewards versus losses) in a gambling-related context.

Dysregulated anticipatory processing in both substance and non-substance addictions may relate to important clinical targets (e.g., cravings, urges or pro-motivational drives). In PG, pro-motivational mechanisms may involve a specific hypersensitivity to the prospect of gambling-related rewards, more so than monetary rewards earned outside a gambling context (Balodis et al., 2012). The extent to which such alterations might contribute to harmful gambling behaviors, including loss-chasing and prolonged gambling sessions, warrants direct examination.

This heightened anticipatory response to possible gambling-related rewards (i.e., risky and uncertain monetary rewards) does not appear to generalize to CD. Rather, CD participants displayed a hypersensitive anticipatory response to impending certain-loss outcomes. Reduced loss-anticipation activity in reward circuitry of cocaine users has been previously reported outside of a gambling context (Patel et al., 2013). From the perspective of pro-motivational mechanisms, these findings suggest anticipatory processes with respect to secondary reinforcers in substance-using individuals may be more robustly influenced by the absence of potential monetary rewards (and consequently the absence of primary, drug-related rewards) than the expectation of monetary gains. The findings also suggest a possible mechanism by which individuals with CD might develop problems with gambling (Hall et al., 2000).

4.2. Near-miss and loss outcome processing

We investigated brain activity associated with near-miss processing by isolating two structural components of 'nearness': the slot-machine symbol arrangement of certain-losses (e.g., ABB/ABA vs. ABC), and the temporal notification of loss (e.g., AAB vs. AB). Consistent with previous research (Chase and Clark, 2010; Clark et al., 2009), HC participants exhibited increased activity in the striatal and insular regions following the delivery of near-miss outcomes; however, this was observed only following sequential near-miss outcomes. This suggests the positive reinforcing value of near-miss outcomes in non-addicted populations is limited to temporal delivery of the near-miss, rather than the symbol arrangement alone. Contrary to hypotheses, this response to near-miss outcomes, sequential or non-sequential, was not exaggerated in PG participants, and was not observed in CD participants.

Loss-processing during gambling-related activities may be of particular relevance to PG as the disorder is marked by persistent gambling despite negative consequences of frequent and substantial losses. PG participants relative to CD or HC participants displayed generally blunted loss responses in the current whole-brain analysis, suggesting near-miss and loss outcomes may be less salient in PG. Our clinically defined sample of PG individuals represents a population with extensive gambling histories and thus potentially greater experience with near-miss and losing gambling-related outcomes. Although chronicity of PG was not associated with neural response in the current study, it is possible that repeated exposure to near-miss and loss outcomes influence/blunt responses over time. Further research is needed to better understand the expression of blunted loss processing in PG and how these signals may be associated with increased gambling experience, impaired decision-making, gambling-related cognitions and loss-chasing behaviors.

Similar to activity observed during anticipatory periods, CD relative to HC participants exhibited an exaggerated negative response in reward/reinforcement circuitry following the delivery of certain,

full-loss outcomes. Previous research demonstrates that neural processing of monetary losses more so than rewards differentiates current from former cocaine users (Balodis and Potenza, in press; Patel et al., 2013). Across participant groups, certain-loss processing was not associated with estimated IQ or depressive symptoms in identified regions, suggesting group differences following the delivery of certain-losing outcomes may not be significantly related to cognitive impairment or mood states. Subjective reports of disappointment and frustration in response to outcomes were not collected, and individuals with CD may find full-loss outcomes less pleasant than individuals with PG and HC participants. Similar to PG participants, CD relative to HC participants did not exhibit exaggerated responses following near-miss outcomes in the current whole-brain analysis. This similarity between PG and CD participants suggests a shared neural mechanism in the processing of losses that may be insensitive to near-miss effects and warrants further investigation.

4.3. Strengths and limitations

Where previous investigations of reward- and near-miss loss-processing in individuals with problematic gambling behavior utilized a correlational design in individuals reporting a range of problem-gambling severity (SOGS 1 to 19) (Chase and Clark, 2010) and a liberal threshold to define problem-gambling samples (SOGS > 2) (Habib and Dixon, 2010), the current study examined clinically defined samples of PG and CD individuals according to DSM-IV diagnostic criteria. We also isolated two structural features of near-miss outcomes (sequential and non-sequential), and exhibit that the positive reinforcement neural responses previously observed in non-addicted samples is replicated only following delivery of sequential near-miss outcomes.

Although the sample size of 72 individuals is significantly larger than other samples investigated for near-miss processing, there exist smaller samples within each diagnostic group (still considerable at $N = 24$ per group), with a limitation that data were collected across two magnets. Consistent with previous multi-site fMRI research, variance attributed to inter-magnet effects were small in comparison to variance associated with inter-subject differences (Brown et al., 2011; Gountouna et al., 2010). For example, regarding activations following the delivery of winning outcomes in Fig. 2, between-subject variance accounted for 31.4% of total variance while within-subject (i.e., between-run) variance accounted for 3.1%, and between-magnet differences accounted for 2.2% of total signal variance, with 63.4% of variance unexplained. These variance estimates are comparable with previous research and suggest any differences between magnets did not significantly contribute to reported results.

CD participants were not well-matched on age and IQ to PG or HC participants; however, there was no evidence that these differences impacted significant findings. The slot-machine design may limit the generalizability of the current findings to commercial EGMs which typically have more rapid rates of play and integrate more complex features. Given observations of impaired delayed-reward processing in addicted populations (Camchong et al., 2011; Miedl et al., 2012), the influence of extended delays in the current task requires additional research. We also did not collect subjective experiences of 'closeness', frustration, or desire to continue gambling during task performance in order to simulate real-world gambling conditions as closely as possible. Furthermore, no relationships between brain activity and measures of impulsivity, problem-gambling severity, or gambling-related cognitions (when controlling for group differences in these domains) were observed. Finally, although results from whole-brain analyses are presented at cluster-level-corrected and -uncorrected thresholds, alternative approaches such as a region of interest analyses may be sensitive to less spatially extensive, localized changes in BOLD signal and identify additional group differences in brain activity. Future directions may also examine circuitry common to both reward- and loss-processing (Liu et al., 2011) and how these mechanisms may be altered in individuals with addictions.

4.4. Conclusions

Individuals with PG and individuals with SUDs share common alterations in reward/loss processing. In the context of slot-machine gambling, PG and CD participants exhibited altered anticipatory and loss-related processing relative to non-addicted comparison participants. Previous neurobiological evidence and high-rates of co-occurring PG and CD suggest a shared vulnerability between these disorders. Distinct alterations in reward/loss anticipation processing may reflect context-driven divergence from an intermediate phenotype in PG and CD. Continued research investigating reinforcement mechanisms in PG and SUDs, as well as in vulnerable and at-risk populations, may provide further insight toward the development of targeted prevention and intervention strategies.

Author disclosures

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Contributors

Drs. Worhunsky, Rogers and Potenza conceptualized and designed the study. All authors contributed to study implementation. Drs. Worhunsky, Mailson and Potenza supervised participant recruitment and data collection. Drs. Worhunsky, Rogers and Potenza contributed to and supervised data analyses. Dr. Worhunsky authored the initial draft and Drs. Malison, Rogers, and Potenza provided additional critical interpretation, feedback, and edits to the manuscript. All authors approved the final manuscript.

Conflict of interest statement

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Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2014.09.013.

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