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A bias towards natural rewards away from gambling cues in gamblers undergoing active treatment

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ABSTRACT

Background: Disorders of substance and behavioral addiction are believed to be associated with a myopic bias towards the incentive salience of addiction-related cues away from general rewards in the environment. In non-treatment seeking gambling disorder patients, neural activity to anticipation of monetary rewards is enhanced relative to erotic rewards. Here we focus on the balance between anticipation of reward types in active treatment gamblers relative to healthy volunteers.

Methods: Fifty-three (25 gambling disorder males, 28 age-matched male healthy volunteers) were scanned with fMRI performing a Monetary Incentive Delay task with monetary and erotic outcomes.

Results: During reward anticipation, gambling disorder was associated with greater left orbitofrontal cortex and ventral striatal activity to erotic relative to monetary reward anticipation compared to healthy volunteers. Lower impulsivity correlated with greater activity in the dorsal striatum and dorsal anterior cingulate cortex to erotic anticipation in gambling disorder subjects. In the outcome phase, gambling disorder subjects showed greater activity in the ventral striatum, ventromedial and dorsolateral prefrontal cortex and anterior cingulate cortex to both reward types relative to healthy volunteers.

Conclusions: These findings contrast directly with previous findings in non-treatment seeking gambling disorder. Our observations highlight the role of treatment state in active treatment gambling disorder, emphasizing a potential influence of treatment status, gambling abstinence or cognitive behavioral therapy on increasing the salience of general rewards beyond that of gambling-related cues. These findings support a potential therapeutic role for targeting the salience of non-gambling related rewards and potential biomarkers for treatment efficacy.

Keywords:

Gambling disorder; fMRI; MID task; reward dissociation; striatum; orbitofrontal cortex

1. INTRODUCTION

Disorders of substance and behavioral addiction are commonly characterized by an incentive bias towards addiction-related cues away from general or natural rewards. This bias has mechanistic roots in addiction theories of incentive salience and reward deficiency (Goudriaan et al., 2004; Sescousse et al., 2013a; Ruth J van Holst et al., 2010). A compelling theory underlying disorders of addiction is that of incentive salience in which motivational biases to addiction-related cues overrides the incentive value over other general rewards (Goldstein et al., 2007; Goldstein and Volkow, 2002). Although this bias in the balance between reward types is a common notion, in fact, few studies in addiction disorders have directly compared cognitive processes underlying these reward types. Here we examine the relative balance between reward types in gambling disorder (GD), a behavioral addiction that has been suggested to represent a useful model of addiction processes without the potential confounding effects of repeated substance misuse on brain function (Fineberg et al., 2014; R J van Holst et al., 2010).

An extensively validated fMRI paradigm (B. Knutson et al., 2001; Brian Knutson et al., 2001; Knutson et al., 2003, 2000; Lutz and Widmer, 2014) (for review see (Knutson and Greer, 2008)) used to examine reward processing is the monetary incentive delay (MID) task. The task allows parsing of processes into reward anticipation and outcome phases. A meta-analysis of the MID task emphasized the role of the ventral striatum (VS) in monetary reward anticipation, and the ventromedial prefrontal cortex (vmPFC) in reward outcome, with the anterior insula and dorsal striatum similarly implicated across both processes (Knutson and Greer, 2008). The findings in the MID task in disorders of addiction are highly inconsistent with a meta-review emphasizing discrepant findings in anticipatory signaling in the VS with predominantly decreases in anticipatory activity reported to monetary outcomes with reports of mixed findings with increased anticipatory activity (Balodis and Potenza, 2015). MID studies in addictions have focused predominantly on monetary reward outcomes, which may contribute to the ambiguity in representing both a conditioned reinforcer and hence a potential drug-related cue and a general reward.

In contrast, studies in behavioral addictions have made attempts to dissociate the anticipation of differential reward types. GD subjects commonly show increased activity to monetary cues in reward-related brain regions (Crockford et al., 2005; Goudriaan et al., 2010; Sescousse et al., 2013a; van Holst et al., 2012). Using a modification of the MID task, GD subjects show greater VS activity to monetary reward anticipation relative to erotic, correlating with both gambling severity as well as reduced behavioral motivation, or prolonged reaction times (RTs), for erotic rewards (Sescousse et al., 2013a). In the reward outcome phase, orbitofrontal cortex (OFC) activity was linked to erotic reward outcomes in both GD and healthy volunteers (HV) but was further recruited by monetary reward outcome solely in GD subjects. The study emphasizes the role of the monetary reward as a conditioned reinforcer hence acting to enhance incentive salience of the gambling-related cue with diminished processing of the non-salient general or natural reward outcome. In a recent similar fMRI study using the MID task, subjects with problematic pornography use, relative to HV, exhibited greater VS responses to erotic as compared to monetary anticipation, suggesting again outcome specificity (Gola et al., 2017).

Here we sought to assess the relative balance between reward types in GD subjects undergoing active treatment using a modified MID task testing both monetary and reward outcomes. We test a larger sample size and focus on a group of GD subjects undergoing active treatment as compared to an untreated active GD group (Sescousse et al., 2013a). We focused on the VS (Knutson and Greer, 2008) hypothesizing enhanced activity during anticipation of monetary relative to erotic rewards in GD compared to HV.

2. RESULTS

2.1 Behavioral

Compared with HV, GD subjects had increased scores on gambling, pornography craving, impulsivity (and two of its subcomponents), depression, anxiety, and decreased digit span (Table 1). When examining RT differences, we found no main effect of Group. When comparing RTs to erotic versus monetary reward types across groups, we found a main effect of Reward, with lower RTs to erotic versus monetary cues in both GD subjects and HV ($F (1,92) = 4.020$, $P = 0.047$). We found no interaction effects in RT differences as a function of Group × Reward.

Table 1: Subject characteristics

Variable	Healthy volunteer subjects	Gambling disorder subjects	Group Comparison
Age	26.8 (5.8)	27.9 (9.3)	t(46) = 0.63 P = 0.53
DART	27.9 (6.6)	25.9 (7.7)	t(46) = 1.39 P = 0.17
Digit span test	16.5 (3.0)	14.3 (3.1)	t(46) = 2.10 P = 0.04*
SOGS	0.4 (0.8)	11.1 (2.8)	t(46) = 17.64 P = 0.00*
PCQ	4.1 (1.2)	5.0 (1.4)	t(42) = 2.10 P = 0.04*
UPPS-P total	131.2 (20.3)	148.6 (19.6)	t(46) = 3.62 P = 0.00*
Negative Urgency	24.4 (5.5)	35.0 (5.8)	t(46) = 6.90 P = 0.00*
Lack of Perseverance	19.3 (3.8)	20.4 (4.1)	t(46) = 1.72 P = 0.09
Lack of Premeditation	22.8 (5.6)	24.6 (5.7)	t(46) = 1.48 P = 0.15
Sensation Seeking	37.3 (4.6)	33.6 (7.6)	t(46) = 1.49 P = 0.14
Positive Urgency	27.4 (7.8)	35.1 (9.6)	t(46) = 3.63 P = 0.00*
BDI	7.2 (8.5)	15.2 (10.7)	t(46) = 3.10 P = 0.00*
STAI	66.8 (17.4)	81.5 (16.3)	t(46) = 3.31 P = 0.00*
AUDIT	7.9 (3.9)	7.1 (4.7)	t(46) = 0.19 P = 0.85
DAST	0.7 (0.9)	0.9 (1.3)	t(46) = 0.49 P = 0.63
FTNA	0.7 (1.7)	1.4 (2.5)	t(46) = 1.26 P = 0.21
Monetary RT	441.8 (32.8)	454.6 (47.7)	t(46) = 0.42 P = 0.67
Erotic RT	456.0 (32.5)	473.3 (44.1)	t(46) = 0.94 P = 0.35
Neutral RT	492.0 (37.9)	522.4 (63.9)	t(46) = 1.52 P = 0.13
Erotic Liking	6.1 (1.1)	6.0 (1.8)	t(46) = 0.69 P = 0.49
Erotic Wanting	5.7 (1.3)	5.7 (2.3)	t(46) = 0.45 P = 0.66

All values are mean (SD). Groups were compared using independent two sample t-tests. Due to a technical error, PCQ was not collected for three healthy volunteers and one gambling disorder subject. Significant group differences are marked with an asterisk (*).

Abbreviations: SD, standard deviation; DART, Danish Adult Reading Test; SOGS, South Oaks Gambling Scale; PCQ, Pornography Craving Questionnaire; UPPS-P, see Table 1 below abbreviation; BDI, Beck's Depression Inventory; STAI, State-Trait Anxiety Inventory; AUDIT, Alcohol Use Disorder Identification Test; DAST, Drug Abuse Screening Test; Profile of Mood States (POMS) nicotine using (FTNA), Fagerström Test for Nicotine Addiction; RT, reaction time.

Table 2: Neuroimaging results

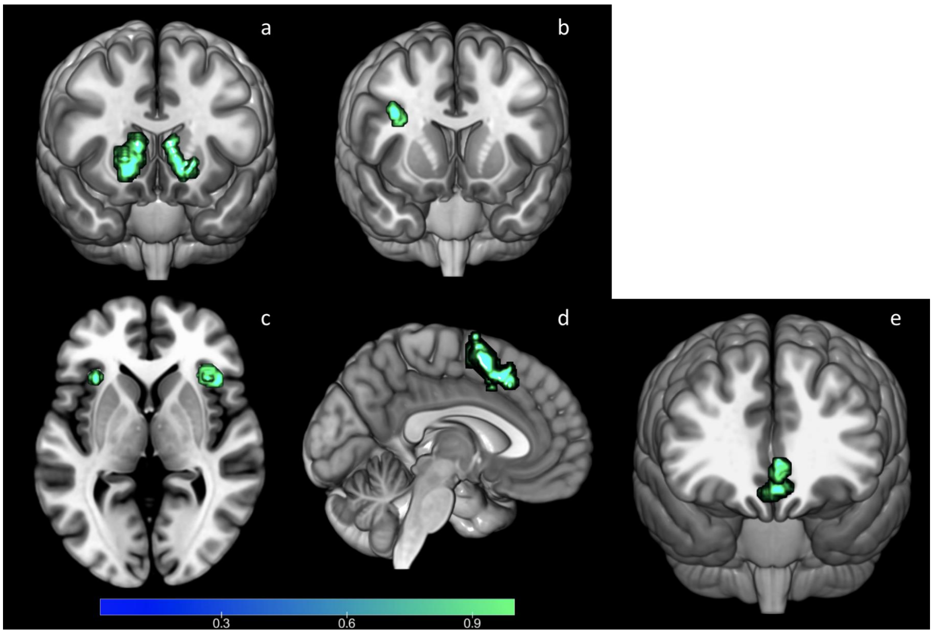
Condition	Phase	Region	FWE-corr. clust.	k_E clust.	T peak	$Z_{\equiv}$ peak	MNI mm mm mm
Erotic > Money	Anticipation	vmPFC (ROI)	0.004	20	4.28	4.19	-2 48 -20
Erotic < Money	Anticipation	l VS	0.000	181	6.03	5.80	-10 12 -6
Erotic < Money	Anticipation	r VS	0.000	442	6.25	6.00	10 10 -4
Erotic < Money	Anticipation	l caudate	0.000	181	6.03	5.80	-8 4 10
Erotic < Money	Anticipation	r caudate	0.000	442	6.25	6.00	10 4 10
Erotic < Money	Anticipation	l putamen	0.000	181	6.03	5.80	-14 8 -8
Erotic < Money	Anticipation	r putamen	0.000	442	6.25	6.00	20 12 -2
Erotic < Money	Anticipation	l anterior insula	0.000	47	5.66	5.47	-34 22 4
Erotic < Money	Anticipation	r anterior insula	0.000	150	5.95	5.73	36 24 -4
Erotic < Money	Anticipation	r dlPFC	0.000	80	5.88	5.67	36 34 22
Erotic < Money	Anticipation	dACC	0.000	715	5.72	5.52	4 20 48
↑ erotic GD × ↓ money HV	Anticipation	l OFC	0.027	238	4.46	4.36	-40 36 -16
↑ erotic GD × ↓ money HV	Anticipation	r VS (ROI)	0.008	7	3.60	3.55	10 10 -4
↑ premeditation × ↑ erotic (GD)	Anticipation	l caudate	0.015	112	7.12	4.91	-18 14 16
↑ premeditation × ↑ erotic (GD)	Anticipation	l putamen	0.000	1222	5.54	4.22	-28 10 10
↑ premeditation × ↑ erotic (GD)	Anticipation	dACC	0.000	498	6.26	4.56	-6 12 48
↓ PCQ × ↑ erotic (GD)	Anticipation	r dlPFC	0.017	112	5.98	4.38	26 48 34
GD > HV	Outcome	vmPFC	0.000	577	3.83	3.77	-4 42 -10
GD > HV	Outcome	l dlPFC	0.003	353	4.16	4.08	-6 44 42
GD > HV	Outcome	vACC	0.000	577	4.75	4.64	-8 34 6
GD > HV	Outcome	l VS (ROI)	0.008	6	3.42	3.37	-10 12 -6
GD > HV	Outcome	r VS (ROI)	0.009	4	3.43	3.38	10 10 -4
Erotic > Money	Outcome	vmPFC	0.000	267	6.99	6.65	-2 44 -18
Erotic > Money	Outcome	l amygdala	0.000	419	9.28	Inf.	-20 -6 -18
Erotic > Money	Outcome	r amygdala	0.000	277	10.80	Inf.	20 -4 -18
Erotic > Money	Outcome	l OFC	0.000	137	7.04	6.69	-32 32 -18
Erotic > Money	Outcome	r OFC	0.034	1	4.83	4.71	32 32 -20
Erotic > Money	Outcome	l FFA	0.000	11895	14.56	Inf.	-48 -58 2
Erotic > Money	Outcome	r FFA	0.000	11895	14.56	Inf.	54 -71 0
Erotic < Money	Outcome	r dlPFC	0.000	207	5.61	5.42	6 40 26

Abbreviations: HV, healthy volunteers; GD, gambling disorder subjects; l, left; r, right; vmPFC, ventromedial prefrontal cortex; ROI, region-of-interest; VS, ventral striatum; dlPFC, dorsolateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; OFC, orbitofrontal cortex; vACC, ventral anterior cingulate cortex; FFA, fusiform face area.

2.2 Anticipation

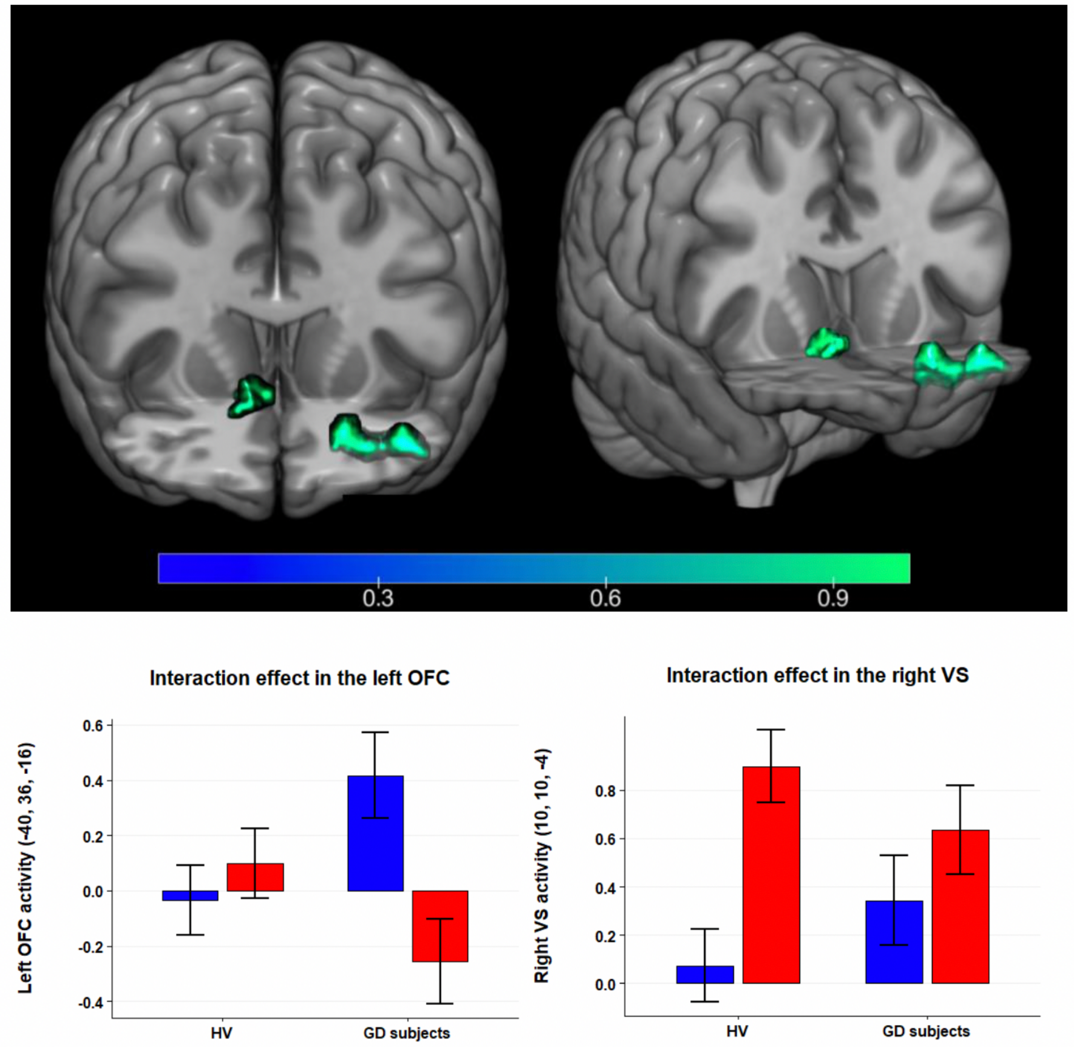
The main effect of Group for the anticipation phase showed that GD relative to HV subjects had greater left parahippocampal and dorsomedial cerebellar activity (all activations in the following are reported for FWE $P<0.05$ cluster corrected unless indicated otherwise for VS ROIs) (see Table 2; for full information, see Table S1). In the main effect of Reward, increased monetary versus erotic anticipation showed greater activity in bilateral VS, caudate, putamen, dACC and bilateral anterior insula, and the right dlPFC, whereas increased erotic versus monetary anticipation showed greater vmPFC activity (Figure 2). The Group × Reward interaction effect showed greater activity to erotic versus monetary anticipation in GD subjects as compared to HV in left orbitofrontal cortex (OFC) on whole brain analysis, and an ROI analysis showed the same Group × Reward interaction effect in the right VS (Figure 3). No correlation was found with these effects with SOGS. The premeditation factor of the UPPS-P revealed a significant negative correlation with activation in the left caudate, left putamen and the dACC to erotic anticipation in GD subjects. PCQ scores also correlated negatively with activation in the right dlPFC within GD subjects (Figure S1).

Figure 2:



Main effect of Reward with greater monetary relative to erotic anticipation activity in (a) bilateral ventral striatum, caudate, and putamen, (b) right dorsolateral prefrontal cortex, (c) bilateral anterior insula, and (d) dorsal anterior cingulate cortex, and with greater erotic relative to monetary anticipation activity in (e) ventromedial prefrontal cortex. For illustration purposes, the image was thresholded at the whole-brain level of p = 0.005 uncorrected and made in MRIcroGL (ver. 1.150909) by manually extracting cluster from Statistical Parametric Mapping and adding an overlay illustrating signal intensity.

Figure 3:



Group × Reward interaction effect with increased erotic versus monetary anticipation in gambling disorder subjects compared to healthy volunteers in the right ventral striatum and left orbitofrontal cortex. Erotic/monetary rewards plotted in blue/red, respectively.
Image thresholded at the whole-brain level of p = 0.001 uncorrected, and made in MRIcroGL (ver. 1.150909) by manually extracting cluster from Statistical Parametric Mapping and adding overlays illustrating signal intensity

2.3 Outcome

The main Group effect of outcome showed greater activity to both reward outcomes in GD subjects relative to HV in the vmPFC, the left dlPFC, and the ventral anterior cingulate cortex (vACC) (see Table 2; for full information, see Table S1), and ROI analyses of the main Group effect showed greater bilateral VS activity in GD compared to HV (Figure S2). The main effect of Reward showed differential patterns of activity across erotic and monetary reward anticipation. Here, erotic outcomes had greater activity in the vmPFC, bilateral amygdala, bilateral OFC, and fusiform face area (FFA), and conversely, the main effect of Reward in monetary outcomes showed greater activity in the right dlPFC. No interaction effects of Group × Reward were found. Adding SOGS scores as a covariate revealed no correlation with this effect

3. DISCUSSION

We show that GD subjects undergoing active treatment had greater left OFC and VS activity to erotic relative to monetary anticipation compared to HV. This effect was unexpected contrasting with previous reports in non-treatment seeking GD which show the opposite findings (Sescousse et al., 2013a). Furthermore, lower impulsivity or specifically the subscale of lack of premeditation correlated with greater activity in dorsal striatum and dACC to erotic anticipation in GD subjects. In the outcome phase, a main group effect was observed with GD subjects relative to HV showing greater reward outcome activity across both reward types across a range of regions including vmPFC, left dlPFC, and the vACC, as well as the bilateral VS.

Our main observation of increased monetary anticipation in HV and erotic anticipation in GD subjects diverged from our hypotheses (Sescousse et al., 2013a). Our findings show a neural bias towards natural rewards (erotic) away from monetary rewards which may act as secondary reinforcers closer to gambling-related cues. Primary rewards such as erotic stimuli have implicated posterolateral OFC (Sescousse et al., 2010) and secondary rewards such as monetary stimuli have implicated the anterolateral OFC (Sescousse et al., 2013b). The OFC coordinates in this current study lie in the posterolateral OFC, similar to a previous study linking posterolateral OFC with erotic reward outcome processing (coronal slice: Y = 32 vs 33 in (Sescousse et al., 2010)). In GD subjects, the OFC has also been implicated in impulsive and risky decision making processes (Cavedini et al., 2002; Lawrence et al., 2009). One plausible reason for the discrepant findings from the hypothesis was that the previous study involved only non-treatment seeking GD subjects whereas this current study involved only GD subjects undergoing active treatment, who were amid 3 months of cognitive behavioral therapy (CBT). Here we show a decrease in the salience of the monetary conditioned reinforcer and an increase in the salience of natural rewards. The difference in findings may be related to the treatment stage which itself may be secondary to the willingness to undergo treatment, the abstinence from gambling or the CBT itself. Those willing to undergo treatment may also represent a very different group and already have shifted their reward balance prior to entering therapy relative to active gamblers. These processes may exert its influence on the relative reward balance by perhaps emphasizing the role of natural or non-gambling related rewards in the environment such as family, social interactions or work or non-drug related activities. CBT emphasizes the recognition of gambling triggers and methods to avoid acting on urges triggered by drug cues including distraction and inhibition training and hence enhance the implicit avoidance of gambling-related cues during active treatment. Indeed, it can be argued that one of the implicit goals of therapy is to decrease the myopic incentive salience assigned to gambling cues and enhance the salience of general or natural rewards in the environment.

Such a mechanism is consistent with our exploratory findings on impulsivity in GD: a subcomponent of impulsivity (lack of premeditation) correlated negatively with erotic reward anticipation in dorsal striatal regions and the dACC. Thus, lower impulsivity was associated with greater anticipation of natural rewards in keeping with a potential shift in impulse control secondary to the effect of CBT on GD treatment. Similarly, the pornography craving scores in GD subjects also correlated negatively with activity in the right dlPFC to erotic anticipation, in line with the role of the dlPFC in cognitive control (MacDonald et al., 2000). Thus, the previous findings might suggest that active maintenance of gambling supports incentive salience theories of enhanced bias to gambling-related cues and reward deficiency theories of decreased neural activity to natural rewards. In contrast, our findings in GD subjects undergoing active treatment challenge these observations. Our findings challenge in particular the stability of the reward deficiency theory and highlight the importance of differing treatment stages of GD in study outcomes. That GD subjects were within three months of the CBT program emphasizes the likely very important effect of treatment group differences, abstinence or the fairly rapid influence of CBT. Studies across different treatment stages in disorders of substance addiction may be more consistent as the effect of repeated substance exposure as compared to gambling behavior exposure on neural processes may be more prolonged in substance addictions. As this current study is cross-sectional and cannot specifically address the underlying mechanisms, further longitudinal studies are required to further address such questions.

In the outcome phase, GD subjects showed a main group effect of greater activity to any reward in the vmPFC, the left dlPFC, the vACC, and bilateral VS, again contrasting with a previous observation of enhanced OFC activity specifically to monetary relative to erotic outcomes in GD (Sescousse et al., 2013a). Our findings argue against the stability of the reward deficiency hypothesis in behavioral addictions suggesting rather generalized enhanced sensitivity to reward outcomes in GD subjects undergoing active treatment.

We further dissociated the influence of anticipation of monetary and erotic rewards across all subjects. The anticipation of erotic relative to monetary rewards was associated specifically with greater vmPFC activity, a region implicated in the processing of primary rewards such as taste (O'Doherty et al., 2002), olfaction (Anderson et al., 2003), auditory (Blood and Zatorre, 2001) and visual (Aharon et al., 2001) feedback, as well secondary rewards such as monetary outcomes (Elliott et al., 2000; Knutson et al., 2000). The vmPFC is suggested to be associated particularly with the emotional components of sexual arousal rather than its cognitive, motivational or physiological components (Ferretti et al., 2005; Karama et al., 2002).

We did not show any RT differences as a function of Group × Reward, which was observed in the previous GD study (Sescousse et al., 2013a). This might suggest that neural activity may be more sensitive to change following treatment intervention with behavioral findings slower to be affected.

There are several limitations to this study. Although we suggest a potential role for either acceptance of treatment or the role of CBT, we did not have specific information on the duration of the CBT beyond that all subjects were in an active 3-month CBT program. To address the differences between the two studies, a longitudinal study is required. As there was no correspondence between behavioral and fMRI correlates of reward anticipation, it is difficult to infer causally about the activation differences between GD subjects and HV. Furthermore, we did not directly compare treated and untreated GD subjects. Therefore, the differences observed in our current results and previously reported findings to treatment status must remain tentative. Regarding stimuli material, the neutral cue was represented using the monetary logo, which may have influenced the contrast with the monetary cue relative to the more complex erotic cue; however, as we focus on the anticipation rather than cue phase, this may be less of an issue. Furthermore, the erotic and monetary stimuli can be categorized as high-intensity erotic stimuli and low-intensity monetary stimuli (with respect to the low amounts), respectfully, which can have created bias across the processing of these reward types.

Our findings highlight opposing findings from previous reports (Sescousse et al., 2013a) highlighting a bias towards enhanced anticipation of natural erotic rewards relative to gambling-related monetary rewards in GD subjects undergoing active treatment. We emphasize the discrepant findings may be related to the treatment status of the GD subjects who were undergoing CBT.

4. EXPERIMENTAL PROCEDURE (METHODS)

4.1 Participants

Twenty-five male GD subjects undergoing active treatment were recruited via the Danish Centers of Pathological Gambling. Twenty-eight age matched male HV were recruited via advertisements including television, newspapers, university notices, as well as social media portals for university students. HV were screened by a psychologist. GD subjects were screened by an expert clinician in order to ensure they fulfilled diagnostic criteria for GD (Del Barrio, 2016). Gambling severity was assessed using the South Oaks Gambling Screen (SOGS) (Lesieur and Blume, 1987). Given the nature of the sexually explicit material presented, all participants were male and heterosexual. Participants were further screened for compatibility with the MRI environment (Schmidt et al., 2016). HV were included if they were between 18-50 years of age, free of psychiatric illnesses or substance or behavioral addictions, as well as meeting MRI safety criteria. The MRI safety criteria was assessed to screen for compatibility with the MRI environment, including having no surgically placed metals (i.e., aneurysm clips, other metal clips, shunts, stents, coils, dental implants, ear implants), shrapnel, electronic implants (i.e., pacemakers; neurostimulators), or claustrophobia. Furthermore, we removed all metallic devices from participants, such as piercings, credit cards, watches, phones, and keys. Prior to scanning, subjects were asked, whether they wished to be informed findings of brain anomalies, excluding tumors and aneurysms. GD subjects were included if they were between 18-50 years of age, had no history of substance use disorders (SUD), including using illicit substances such as cannabis, or major psychiatric disorders (including current moderate/severe major depression).

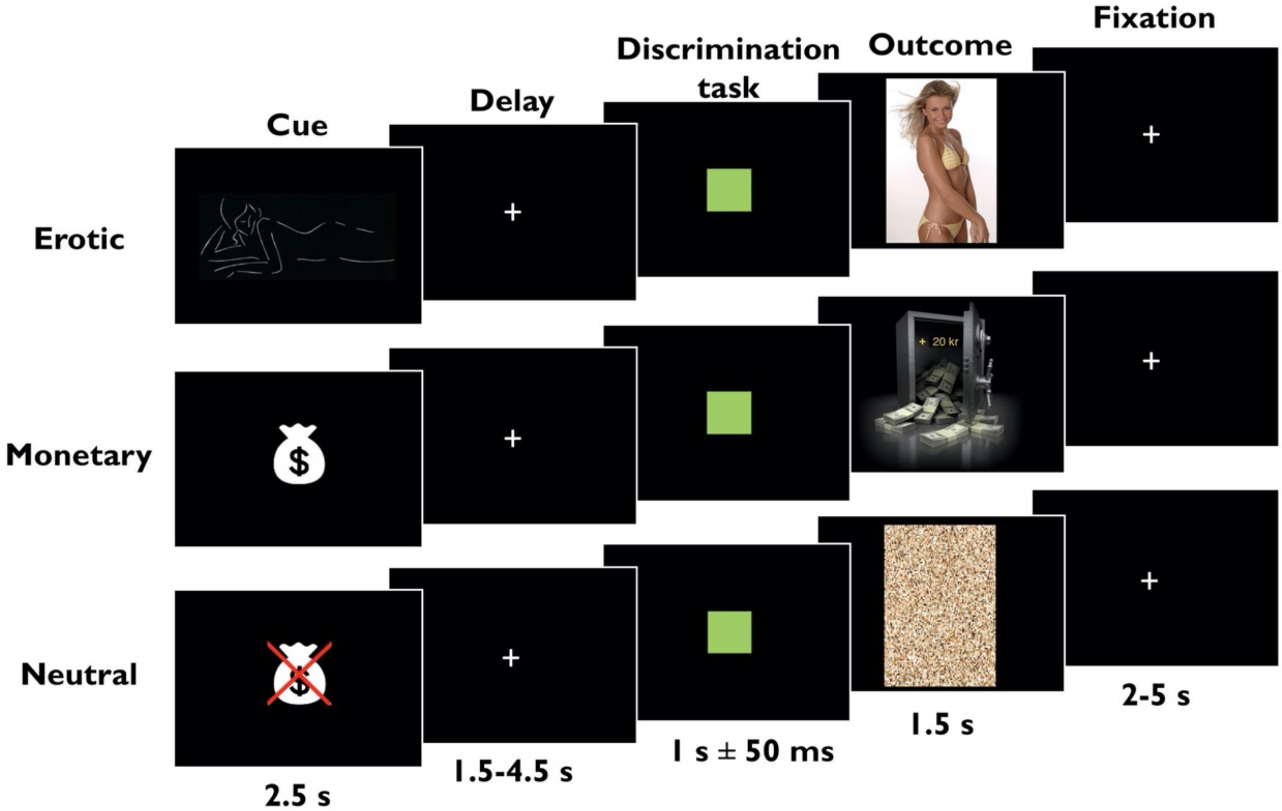
Participants were screened by a trained psychologist, completing questionnaires on impulsivity using the UPPS-P questionnaire (Lynam et al., 2006), depression using Beck's Depression Inventory (BDI) (Dozois, 2010), gambling using the SOGS (Lesieur and Blume, 1987), pornography craving using the pornography craving questionnaire (PCQ) (Kraus and Rosenberg, 2014), nicotine using Fagerström Test for Nicotine Addiction (FTNA) (HEATHERTON et al., 1991), alcohol using Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993), illicit substance use using Drug Abuse Screening Test (DAST-20) (Skinner, 1982), and anxiety using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). Short-term memory was assessed using a digit span test from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2014) and IQ using a Danish version of the National Adult Reading Test (DART) (Nelson and Willison, 1991).

Written and informed consent for participation were collected for all participants. The study was approved by the Middle Jutland Scientific Ethical Committee. All participants were paid for their participation. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

4.2 Task

All participants completed a modified reward-generalized version of the MID task (Figure 1) consisting of monetary, erotic and neutral reward outcomes (Sescousse et al., 2013a). The MID task requires an individual to react to a target stimulus presented after an incentive cue to win the indicated reward. In doing so, this paradigm allows the detailed examination of different phases of reward processing such as reward anticipation and outcome processing, as well as the processing of tasks under different reward conditions. Each trial consisted of four different phases of reward cue, reward anticipation, discrimination task, and reward outcome. The cue indicated the type of reward represented by an appropriate symbol of the reward type. Anticipation was represented using a fixation cross during a variable delay period. Participants then performed a visual discrimination phase where each correct response subtracted 50 ms from the allowed response time, and each incorrect response added 50 ms. Success in the form of a correct response within the response time led to the outcome (e.g., a sexually explicit image or a monetary amount, representing erotic and monetary reward, respectively) and slow or incorrect responses led to reward omission. No reward (neutral) trial was represented using scrambled pictures of the sexually explicit ones to control for visual processing of color, complexity, and size. The erotic stimuli for the task were chosen from a validated stimuli set (Gola et al., 2017) (24 pictures of unclothed women were used), whereas monetary rewards was represented by an indicator of the amount won (an equal amount of 10 or 20 Danish kroner), along with the cumulative winnings during the task. Ratings of each erotic image were introduced after the task was completed to avoid desensitization of the sexually explicit stimuli material. The ratings accounted for the variability in sexual preferences, and to assess the level of liking (pleasantness) and wanting (sexual arousal) from the erotic images.

Figure 1:



The monetary incentive delay task. Participants were first shown a cue indicating the reward type of an upcoming reward. The cue was then replaced by a fixation cross, where subjects anticipated reward and prepared for a task. After the anticipation phase, participants were to perform a discrimination task, in which a correct response (button press to a symbol within 1 second) was needed to obtain the reward. In correct and rewarded trials, subjects were shown either a safe with information about the amount won and cumulative winnings, or a sexually explicit picture of an unclothed woman.

4.3 Neuroimaging

4.3.1 Data acquisition and processing

All MR data were collected using a Siemens Skyra 3T scanner with a 32-channel head coil at the Centre of Functionally Integrative Neuroscience (CFIN) at the Danish Neuroscience Centre in Aarhus Denmark. The sequences used during the scan were a field map acquisition (multi-band, single-echo) and a structural T1-weighted MP2RAGE sequence (Moeller et al., 2010; Setsompop et al., 2012). The echo-planar imaging (EPI) sequence was 1200 volumes (repetition time (TR): 1660 ms, echo time (TE): 30 ms, flip angle: 75°, acquisition matrix: 106×106×72).

Preprocessing of the functional EPI images used Statistical Parametric Mapping 12 (SPM) (Penny et al., 2007). Converted NIFTI images were slice time corrected to the center of each TR period, realigned, co-registered to the same EPI image from SPM using OldNormalise (chosen based on three comparisons of registration and normalization, including T1, field-map and EPI images as it gave a higher spatial resolution in orbito- and medial frontal regions when compared with field map and segmentation-based methods) (Calhoun et al., 2017). Images were then smoothed with a full width at half maximum (FWHM) kernel of 6 mm^3. In the model specification for first-level analysis, realignment parameters were included as a covariate. We modelled all trial components separately including cue, anticipation, response, outcome and inter-trial interval at the first level using a mixed block design including the duration of each event. Second-level analyses were then performed dividing participants into groups based on their blinded scan IDs focusing on the 1.5 to 4.5 second anticipation and 1.5 second outcome phase.

Second-level analyses were computed separately for anticipation and outcome phases using a full factorial design specification, with a between-subjects factor of Group and a within-subjects factor of Reward type. We first tested for main effects of Group and Reward for the two separate phases of anticipation and outcome for HV and GD groups. Where main effects were found in either Group or Reward, subsequent Group × Reward interaction effects were examined with posthoc interaction effects being analyzed with two-sample t-tests if the interaction was significant. The Reward conditions were compared with neutral as the control (e.g., monetary anticipation – neutral anticipation; erotic anticipation – neutral anticipation). On an exploratory level in the second level analysis, regression analyses with questionnaire scores were assessed focusing on the contrasts (e.g., monetary anticipation – neutral anticipation) with questionnaire scores as regressors separately in GD, controls, and as a group. All analyses were reported at whole brain FWE $P<0.05$ cluster corrected (viewed at whole-brain uncorrected with cluster defining threshold of $P<0.001$). Region-of-interest (ROI) analyses focused on the VS, a region implicated in the meta-analysis of MID tasks (Knutson and Greer, 2008) and were conducted with small-volume-correction (SVC) of 5 ^{mm} with significance assigned at FWE $P<0.05$. The coordinates selected for the VS ROIs were based on an activation likelihood estimate (ALE) analysis on reward processing (Knutson and Greer, 2008).

4.3.2 Statistical Analysis of behavioral outcomes

Subjects' characteristics and questionnaire scores were compared between groups with two-tailed t-tests. When comparing RTs to different reward types we compared differences in RTs to erotic and monetary versus neutral with an improved-scoring algorithm developed by Greenwald and colleagues (Greenwald et al., 2003). The algorithm reduces the biases due to variability of RTs by standardizing the differences in response latencies and dividing an individual's difference in RTs by a personalized standard deviation of these differences. We compared Group × Reward RT differences using a two-way ANOVA. All statistical analyses were performed using R (version 3.5.1) (Team, 2014).

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Each author's contributions are listed in the author order using initials to indicate their contributions to (1) Conceptualization; (2) Data curation; (3) Formal analysis; (4) Funding acquisition; (5)

Investigation; (6) Methodology; (7) Project administration; (8) Resources; (9) Software; (10) Supervision; (11) Validation; (12) Visualization; (13) Writing original draft; (14) Review & editing.

CS: 1-14 CG: 3, 6, 9, 11 HS: 2,6,9 TLK; 2,6,9 TEL: 3,9 VV+AM: 1-7, 10, 14.

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