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FULL-LENGTH REPORT

Striatal cue-reactivity and neurotransmitter function in gambling disorder

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ABSTRACT

Background: Abnormal striatal cue reactivity is one of the neurobiological hallmarks of substance use disorders (SUDs). Cue reactivity is associated with relapse, prompting efforts to target its underlying mechanisms with therapeutic interventions. However, the neural correlates of cue reactivity in behavioral addictions, such as gambling disorder (GD), remain poorly understood. Here we investigated striatal cue reactivity and its associations with neurotransmitters in individuals with GD using multimodal neuroimaging. *Methods:* Thirteen subjects with GD and 16 healthy controls (HC) underwent fMRI using a block-design consisting of three different types of visual stimuli: gambling-related, erotic, and neutral videos. The subjects also underwent brain PET imaging with three radiotracers to assess dopamine ([18F]FDOPA), opioid ([11C]carfentanil) and serotonin ([11C]MADAM) function. *Results:* GD subjects showed a significantly greater BOLD response in the dorsal striatum compared to HC when viewing gambling-related versus neutral videos (pFWE<0.05). Enhanced cue-reactivity was specific to gambling, as there were no significant differences between the groups with natural reward cues (erotic vs. neutral videos). The dorsal and ventral striatum BOLD responses to gambling videos were coupled in HC ($r = 0.7$, $p = 0.003$) but not in GD ($r = -0.1$, $p = 0.75$; group difference $p = 0.008$). In GD, dorsal striatal BOLD response to gambling cues correlated with [11C]carfentanil, but not with [18F]FDOPA or [11C]MADAM, binding ($r = 0.8$, $p < 0.001$). *Conclusions:* GD is characterized by increased gambling cue-induced activity in the dorsal striatum, which is linked to mu-opioid receptor availability. The findings highlight the potential role of the mu-opioid system in mediating cue-reactivity in behavioral addictions.

KEYWORDS

gambling disorder, striatum, cue reactivity, opioid system

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INTRODUCTION

Gambling disorder (GD) is characterized by persistent and recurrent gambling despite of harmful consequences (American Psychiatric Association, 2013). The worldwide prevalence of GD has been estimated to be 1.6–1.9% (Shaffer, Hall, & Vander Bilt, 1999; Shaffer & Hall, 2001; Welte, Barnes, Wieczorek, Tidwell, & Parker, 2002, 2015; Welte, Barnes, Tidwell, Hoffman, & Wieczorek, 2015). Clinically, GD shares several features with substance use

disorders (SUDs), including increased impulsivity, compulsive behavior, and the pursuit of rewarding stimuli despite negative consequences (Clark, 2010; Fauth-Bühler, Mann, & Potenza, 2017; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006; Reuter et al., 2005).

Neurobiologically, addictive disorders are linked with striatal dysfunctions. In healthy controls, natural or extrinsic rewards, such as food, sex and money, are associated with hemodynamic responses in the ventral striatum (Diekhof, Kaps, Falkai, & Gruber, 2012; Sescousse, Caldú, Segura, & Dreher, 2013). Reward anticipation in healthy controls has also been associated with increased activation in both the ventral and dorsal striatum, reflecting the coordinated involvement of these regions (Oldham et al., 2018). In SUDs, however, the reward circuitry becomes desensitized leading to reduced ventral striatum responses through continued excessive substance use (Koob & Volkow, 2010). This desensitization is associated with a transition to substance-related cue-induced reactivity in the dorsal striatum along with a blunted reactivity to natural reward cues, leading to ventral-to-dorsal shift in striatal reward-related signaling (Engelmann et al., 2012; Everitt & Robbins, 2005; Sjoerds, Brink, Beekman, Penninx, & Veltman, 2014; Vollstädt-Klein et al., 2010; Zhou et al., 2019). Similar findings have been reported with cue reactivity in GD (García-Castro, Cancela, & Cárdaba, 2023; Starcke, Antons, Trotzke, & Brand, 2018), but the results are not uniform (Balodis et al., 2012; Choi et al., 2012; Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005; Potenza et al., 2003).

Dopamine is one of the key neurotransmitters involved in reward- and cue-induced striatal responses. PET imaging studies in humans have repeatedly demonstrated striatal dopamine release in response to drugs, alcohol and monetary rewards (Hyman, Malenka, & Nestler, 2006; Zald et al., 2004). In SUDs, these dopaminergic responses are blunted, with early studies suggesting an enhanced cue-induced dorsal striatal dopamine release, mediated by baseline dopaminergic tone in the striatum (Volkow et al., 2006; Wong et al., 2006). The findings in GD however differ from those of SUDs by mainly showing increased dopaminergic responses to gambling and no downregulation of post-synaptic dopamine receptors (Boileau et al., 2014; Clark et al., 2012; Joutsa, Johansson, et al., 2012; Linnet, Peterson, Doudet, Gjedde, & Møller, 2010). However, striatal dopamine function is also regulated by multiple other neurotransmitter, including endogeneous opioids and serotonin, but their role in cue-induced striatal responses is largely unstudied (Gago et al., 2007; Majuri, Joutsa, Arponen, Forsback, & Kaasinen, 2018; Tuominen et al., 2015; Unterwald & Cuntapay, 2000). The opioid system contributes to processing of multiple rewards (Nummenmaa & Tuominen, 2018) and opioids also induce pleasure independently of dopamine (Hnasko, Sotak, & Palmiter, 2005). Currently, there is no agreement on the mechanisms underlying cue reactivity in GD, and pharmacological treatments are yet to be established. Identifying the molecular mechanisms associated with cue-reactivity in GD could pave way for discovery new therapeutic options.

This study had two primary objectives: (1) to examine striatal hemodynamic responses to gambling-related cues in individuals with GD compared to healthy controls, and (2) to explore the contribution of striatal dopamine, opioid, and serotonin systems to these cue-induced responses in GD.

METHODS

Subjects

In this study, a total of 32 participants were included, consisting of 15 individuals diagnosed with GD and 17 healthy controls (HCs) who had no history of gambling problems. The groups were age- and sex- matched. The inclusion criteria for the GD group was diagnosis confirmed through clinical interviews utilizing the DSM-IV criteria for pathological gambling but all GD subjects also fulfilled the diagnostic criteria for the most recent diagnostic criteria (DSM-5) for GD. The individuals with GD were not selected based on their preferred gambling activities and all reported engaging with multiple different gambling activities. For HC individuals, the inclusion criteria involved an absence of any gambling problems based on the clinical interview. Participants (from both groups) with the presence of active neurological, or psychiatric disorders (apart from GD in the GD group), evidence of current alcohol or substance use disorder, significant medical conditions, current pregnancy, strong susceptibility to allergic reactions or nausea, body weight exceeding the scanner limit (180 kg), and any contraindications to magnetic resonance imaging, were excluded from the study.

Clinical and behavioral measures

Clinical and behavioral data were obtained through validated questionnaires during a clinical interview at the initial study visit. This information included subject demographics, including age, gender, body mass index (BMI), and smoking status. Additionally, it included gambling-related metrics, such as weekly gambling hours, weekly gambling expenditure, and problematic gambling duration. The administered questionnaires were the South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987), Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996), and Barratt Impulsiveness Scale (BIS-11) (Barratt, 1985).

Image acquisition

Each participant completed an extensive brain imaging protocol, which encompassed structural MRI, task-based functional MRI (task-fMRI), and three distinct brain PET scans designed to assess serotonin ([^{11}C]MADAM), dopamine ([^{18}F]FDOPA), and opioid ([^{11}C]carfentanil) neurotransmission.

MRI. We acquired 3D T1-weighted scans to serve as a structural reference for data analysis. These scans were obtained using a 3T PET-MRI scanner (Philips Ingenuity, Philips Healthcare, Cleveland, OH, USA) equipped with a

34-channel receiving head coil. The scanning protocol employed a sagittal 3D T1-weighted TFE sense pulse sequence with isotropic voxels using the following parameters: TR 8.1 ms, TE 3.7 ms, flip angle 7°, matrix size 256 × 256, and a total of 176 slices.

fMRI video task. fMRI scans were performed using PET-MRI scanner Philips Ingenuity (Philips Healthcare, Cleveland, OH, USA). Anatomical T1-weighted images were collected before fMRI tasks using the same scanner. Blood-oxygenation dependent (BOLD) echo-planar imaging (EPI) was applied. Whole-brain BOLD-weighted EPI sequence sensitive to the BOLD contrast was obtained during the stimuli presentations. The scanning protocol utilized a TR of 2,000 ms, a TE of 20 ms, and a flip angle of 75°. It included 35 slices with a thickness of 4 mm each, operating in parallel multislice mode.

The experiments were run with the classic block design with 10 blocks per condition. Participants were shown videos from three categories: neutral, natural reward (erotic), and gambling-related videos. Neutral videos depicted everyday activities, such as people walking in public spaces. Erotic videos primarily featured "soft-core" heterosexual content, including scenes of nudity and intercourse. All subjects identified themselves as heterosexual, except for one control subject who identified himself as homosexual. Gambling-related videos portrayed individuals engaged in heterogeneous gambling activities, including for example roulette, handling chips, and placing bets. Each category consisted of ten unique video clips from existing movies, which were presented twice in randomized order. Thus, every subject saw altogether 60 video clips with breaks of 6–8 s where participants were watching a black screen. Each video clip lasted approximately 9–14 s. The total stimulus presentation time was approximately 17 min. The schematic study design can be seen in Fig. 1. Due to scanner malfunction, two individuals with GD were not scanned with fMRI. In addition, one HC subject was excluded from the analysis due to lack of occipital BOLD response during the video task, suggesting that this subject was not viewing the videos as instructed. The fMRI paradigm was slightly shorter for three participants because of scanner storage space temporarily running out. To ensure that the shorter paradigm doesn't bias the results, the main results were confirmed excluding these subjects from the analyses.

PET imaging. PET imaging protocols have been previously detailed in (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017). Imaging was conducted using a high-resolution research tomography (HRRT) PET scanner from Siemens Medical Solutions, with an intrinsic spatial resolution of 2.5 mm. Scanning times were 51 min for [^{11}C]carfentanil, and 90 min each for [^{18}F]FDOPA and [^{11}C]MADAM. The 3D mode with scatter correction was applied. All three tracer PET scans were performed during a single day at fixed intervals. Due to logistical issues, three subjects underwent PET scans on two separate days. To minimize head movements during scanning, an individually shaped thermoplastic mask was used except for three GD patients who utilized a Velcro strap due to discomfort with the mask. Head motion was tracked using a stereotaxic infrared camera (Polaris vicar, Northern Digital, Waterloo, Canada).

All PET scans were performed on the same day (except for one [^{11}C]carfentanil and two [^{18}F]FDOPA scans, which were performed on a separate visit due to a scanner malfunction or tracer production failure). The mean (SD) time interval between the fMRI and PET visits was 2.95 (0.99) months. Group differences in PET imaging and resting state connectivity fMRI results from this cohort have been published earlier (Bellmunt-Gil, Majuri, Arponen, Kaasinen, & Joutsa, 2023; Majuri et al., 2018; Majuri, Joutsa, Johansson,

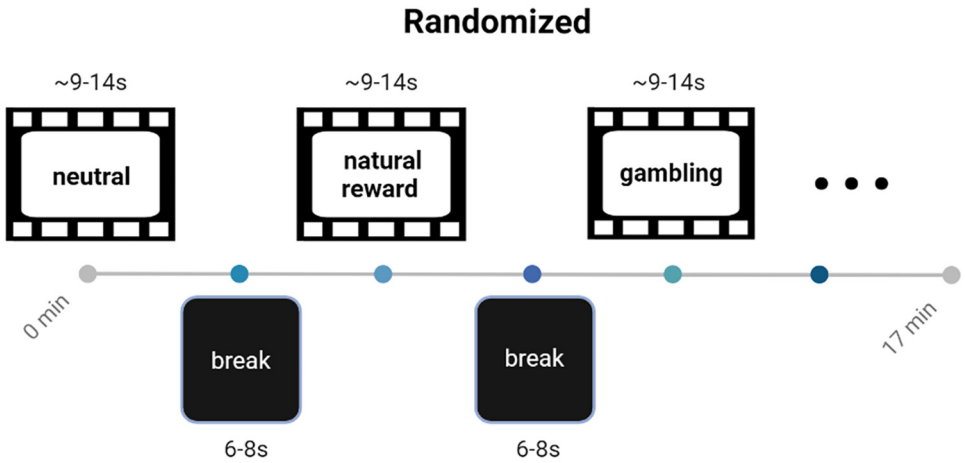

Fig. 1. **Task-fMRI study design**
Block design to study the brain activation patterns while being presented videos of different categories, including gambling, natural reward, and neutral

Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017).

In the [^{11}C]MADAM analysis, two other participants (one with GD and one HC) were excluded due to excessive head movement while scanning and one participant with GD due to the use of SSRI medication (panic disorder in remission). Although the participant was instructed to stop the medication five days prior scanning, the [^{11}C]MADAM uptake was low throughout the brain indicating insufficient washout and the subject was excluded from the analyses to avoid bias. Additionally, technical problems during scanning resulted in the unavailability of one HC for the [^{11}C]carfentanil analysis, and data from one HC along with two GD participants were unavailable for the [^{18}F]FDOPA analysis as described previously (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017).

Task-fMRI data preprocessing and analyses

Anatomical data preprocessing. Anatomical preprocessing was performed with fMRIPrep 23.1.0 (Esteban et al., 2019). The T1-weighted (T1) images were corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (Avants, Epstein, Grossman, & Gee, 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs). Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b017774, Zhang, Brady, & Smith, 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 7.3.2, RRID:SCR_001847, Dale, Fischl, & Sereno, 1999). Volume-based spatial normalization to the Montreal Neurological Institute (MNI) space was performed through nonlinear registration with antsRegistration (ANTs 2.3.3).

Functional data preprocessing and analyses. Functional preprocessing was performed with fMRIPrep 23.1.0 (Esteban et al., 2019). Briefly, the functional preprocessing pipeline involved the following steps: Head-motion parameters were estimated and corrected using mcflirt (FSL, Jenkinson, Bannister, Brady, & Smith, 2002), aligning the BOLD time-series back to its original space. Co-registration between BOLD and T1w references was performed using bbregister (FreeSurfer). Various confounding time-series were derived from the preprocessed BOLD data, including framewise displacement (FD), DVARS, and three global signals (CSF, WM, whole-brain masks). Physiological regressors were also extracted for noise correction using CompCor (tCompCor, aCompCor). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were classified as motion outliers. The preprocessed BOLD runs were resampled into MNI space. The internal operations of fMRIPrep relied on Nilearn 0.10.1 within the functional processing workflow. For more details, refer to fMRIPrep's documentation on workflows.

Individual and group level analyses were performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB (R2021b; MathWorks, Natick, MA, USA). In the first-level analyses, a general linear model (GLM) was used to estimate condition-specific responses to the task. Regressors were constructed for each experimental condition (neutral, gambling, erotic) by convolving the event onsets and durations with the canonical hemodynamic response function. Six rigid-body motion parameters and motion outlier volumes (identified using a framewise displacement threshold of 0.5 mm) were included as nuisance regressors. The voxel-wise group-level analyses we restricted to the striatum by using a striatal mask (Mawlawi et al., 2001) in the second level analyses, as the study was designed to investigate striatal function. Voxelwise Family-Wise Error (FWE) correction was applied with a corrected threshold of $p < 0.05$ was considered significant to control for multiple comparisons in the fMRI data (Eklund, Nichols, & Knutsson, 2016). Age and sex were included as nuisance covariates to the group-level analyses. Striatal masks (ventral and dorsal) and significant clusters, identified in the contrasts of interest in the voxel-wise analyses, were used as regions-of-interests (ROIs) to extract mean beta values for visualization and correlation analyses with clinical and PET imaging data. Pearson or Spearman correlations were used for these analyses, as appropriate.

PET imaging data preprocessing and analyses

PET data preprocessing has been previously documented (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017). Briefly, image realignment and coregistration were performed using SPM8 software in MATLAB R2012a. Individual PET images were realigned to correct for any head movement during scanning, and the scan reconstruction details were as described previously (Johansson, Keller, Tuisku, & Teräs, 2016). Regional data were extracted from regions of interest (ROIs) generated using FreeSurfer's recon-all (version 5.3.0). These ROIs were employed to extract average time-activity courses for modeling. [^{18}F]FDOPA Ki images were computed using a Patlak plot, while [^{11}C]MADAM and [^{11}C]carfentanil BP_{ND} images were calculated using a simplified reference tissue model. The cerebellar cortex served as the reference region for [^{11}C]MADAM, while the occipital cortex was designated for [^{18}F]FDOPA and [^{11}C]carfentanil. Parametric images were normalized to the Montreal Neurological Institute standard space (MNI152) using T1 information with DARTEL and subsequently smoothed with a 6 mm Gaussian kernel for enhanced signal-to-noise ratio in statistical analyses restricted to the striatum (Mawlawi et al., 2001). Two subjects, whose measurements from the right NAcc [^{11}C]MADAM BP_{ND} showed standard deviations greater than 2, were identified as outliers and were excluded from the analyses involving this variable.

To investigate neurotransmitters underlying the identified abnormal functional activation, BP_{ND}/Ki values were extracted from the significant connectivity cluster. In addition, for further analyses, BP_{ND}/Ki values were also obtained

from the dorsal and ventral striatum. To assess the relationship between [^{11}C]carfentanil BP_{ND}, [^{18}F]FDOPA Ki and [^{11}C]MADAM BP_{ND}, and BOLD responses to gambling-related stimuli, we conducted six correlation analyses with both groups applying Bonferroni correction. Significant correlations identified in GD participants were subsequently compared to those of healthy controls to test if the correlations differ significantly between the groups.

Statistical analyses

Statistical analyses for ROI and clinical data were performed using IBM SPSS Statistics, version 27 (Armonk, NY, USA). Group differences in demographic and clinical data were assessed using independent samples *t*-tests, Mann-Whitney tests, and chi-square tests. To explore relationships between clinical/behavioral and/or imaging data, Pearson and Spearman correlation coefficients were used. To analyze if correlations differ significantly between groups (GD/HC) Fisher's *r* to *z* transformation was used.

Ethics

The study protocol received approval from the Ethics Committee of the Hospital District of Southwest Finland. All participants provided written informed consent, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

RESULTS

Demographic and clinical measures

Table 1 presents all demographic and clinical information. No significant group differences were found in age, sex, AUDIT and BIS-11 attention subdomain. The GD group showed significantly higher scores in all gambling-related variables, BIS-11 motor and nonplanning subdomains, and BDI, and were more often smokers compared to the HC group.

Table 1. Demographic and clinical characteristics

Variables (mean ± SD)	GD (n = 13)	HC (n = 16)	p value
Age (years)	43.9 ± 12.2	43.5 ± 11.4	0.94
Sex (male/female)	6/7	8/8	0.84
Gambling hours per week	8.6 ± 6.6	0.6 ± 1.3	<0.001
Gambling euros per week	175.4 ± 146.5	3.7 ± 7.5	<0.001
Problem gambling years	11.9 ± 7	0.0 ± 0.0	<0.001
PG DSM-IV points	7.5 ± 1.5	0.1 ± 0.3	<0.001
SOGS	13.3 ± 2.4	0.1 ± 0.3	<0.001
BIS11_attention	19.5 ± 2.9	17.8 ± 1.9	0.054
BIS11_motor	26.3 ± 2.1	22.3 ± 2.5	<0.001
BIS11_nonplanning	28.4 ± 1.9	23.1 ± 4.6	<0.001
BDI	14.7 ± 8	2.9 ± 3.2	<0.001
Smoking	11/2	6/10	0.01
AUDIT	6.4 ± 4	5.4 ± 3.4	0.45

SD: Standard deviation; GD: Gambling disorder; HC: Healthy controls; AUDIT: Alcohol Use Disorders Identification Test; SOGS: South Oaks Gambling Screen; BIS: Barratt Impulsiveness Scale; BDI: Beck Depression Inventory; PG: Pathological gambling.

Striatal hemodynamic responses to visual stimuli

Individuals with GD showed significantly greater BOLD response in the dorsal striatum than HCs when watching gambling-related versus neutral videos (Fig. 2). Overall, BOLD response in individuals with GD tended to be higher in the dorsal striatum and lower in the ventral striatum (Fig. 2 coronal section). No significant group differences were found in the erotic videos contrasted to gambling or neutral videos (uncorrected voxel-wise maps and anatomical ROI-based parameter estimates for all contrasts are shown in Appendix Figs A1 and A2). The significance of the results did not change when removing the single subject who identified himself as homosexual. Removing the three subjects with shorter fMRI paradigm did not change the results either.

The BOLD response within the dorsal striatum cluster did not significantly correlate with GD symptom severity or other gambling-related variables ($p > 0.18$). In addition, there were no significant correlations between this BOLD response and BDI score ($r = 0.12$, $p = 0.72$), AUDIT score ($r = -0.36$, $p = 0.23$) or smoking ($r = 0.4$, $p = 0.17$).

There was a significant positive correlation between ventral and dorsal striatum BOLD response to gambling contrasted to neutral videos in HCs ($p = 0.003$) but not in individuals with GD ($p = 0.75$). The difference between the correlation coefficients was significant ($p = 0.008$) (Fig. 3).

Neurotransmitter function in the striatum

The ventral and dorsal striatum ROI tracer binding/uptake values are presented in Table 2. There were no significant group differences in the dorsal and ventral striatum in any of the tracers (Table 2).

In individuals with GD, [^{11}C]carfentanil BP_{ND} correlated significantly with BOLD response to gambling contrasted to neutral videos in the dorsal, but not ventral, striatum ROI ($r = 0.81$, $p < 0.001$, Bonferroni corrected $p = 0.004$) (Fig. 4A). In contrast, the dorsal striatum correlation within the HC group was not significant ($r = 0.08$, $p = 0.79$; group difference in the correlation coefficients $p = 0.001$). There were no other significant correlations between any of the other measured neurotransmitters and striatal BOLD response in the dorsal or ventral striatum (Fig. 4).

DISCUSSION

This study has several key findings. First, we observed increased cue-reactivity in the dorsal striatum in GD compared to HCs, specifically in response to gambling-related stimuli. Second, unlike in HCs, the dorsal striatum

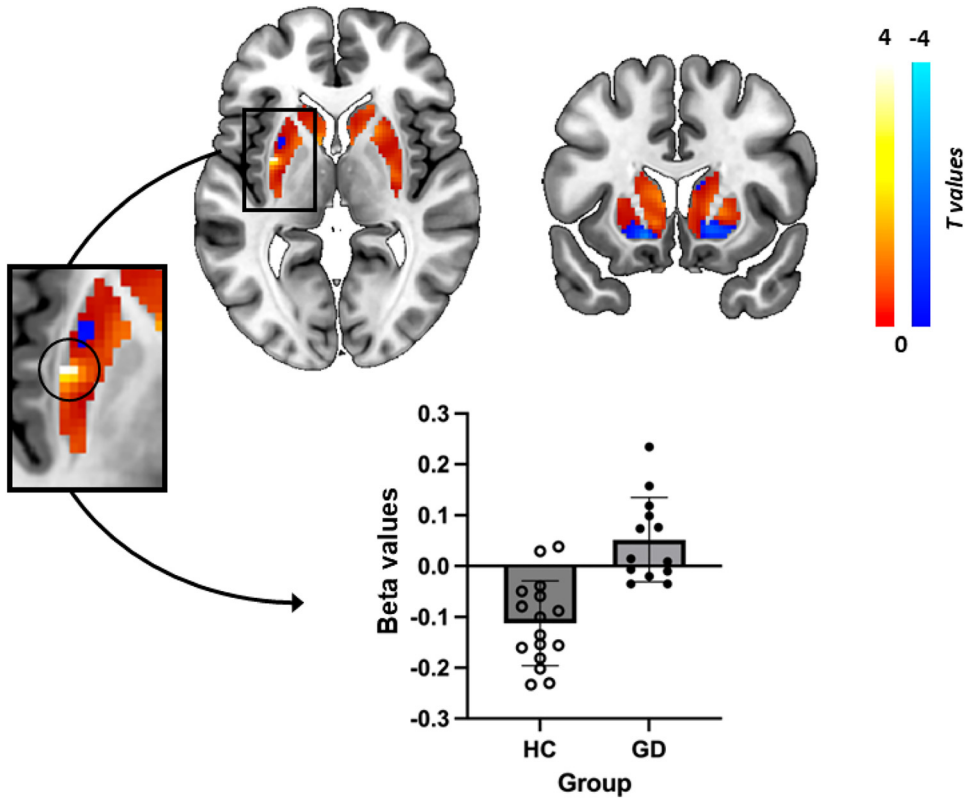

Fig. 2. **Striatal BOLD response to gambling videos in individuals with GD and HC (gambling videos vs neutral videos)** Unthresholded GD > HC BOLD T-map. Significant cluster showed within the zoomed box (peak coordinates at −32 −2 2, cluster size 2 voxels, $P_{FWE} = 0.004$). To illustrate the direction of the effect, the raw values of the significant cluster were plotted (HC: −0.11(0.08), GD: 0.05(0.08))

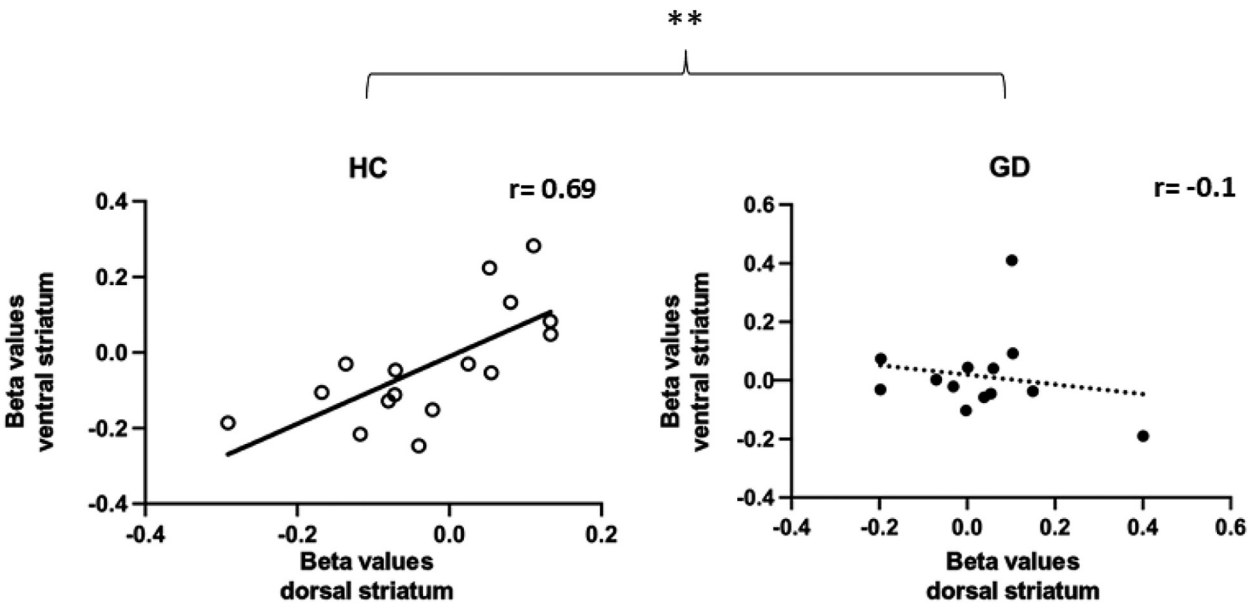

Fig. 3. **Correlations between ventral and dorsal striatum BOLD response to gambling videos** Correlations in healthy controls (HCs) and individuals with gambling disorder (GD). ** represents a significance level of $p \leq 0.01$

responses to gambling cues did not correlate with those in the ventral striatum, suggesting a functional decoupling between these regions during gambling cues. Lastly, in the GD group, the cue-induced dorsal striatum responses were associated with mu-opioid receptor availability, but not with presynaptic dopamine synthesis capacity or serotonin transporter binding, suggesting a unique involvement of the opiod system in mediating these responses.

Table 2. Group comparisons within tracer binding in ventral and dorsal striatum

Tracer and region (mean ± SD)	GD	HC	*p* value
[^{11}C]MADAM (BP_{ND})	*n* = 13	*n* = 16	
Dorsal striatum	0.91 ± 0.13	0.98 ± 0.12	0.15
Ventral striatum	1.14 ± 0.21	1.21 ± 0.15	0.31
[^{18}F]FDOPA (K_i)	*n* = 13	*n* = 16	
Dorsal striatum	0.012 ± 0.002	0.012 ± 0.001	0.68
Ventral striatum	0.01 ± 0.001	0.01 ± 0.001	0.8
[^{11}C]carfentanil (BP_{ND})	*n* = 15	*n* = 16	
Dorsal striatum	1 ± 0.22	1.16 ± 0.28	0.13
Ventral striatum	1.7 ± 0.27	1.84 ± 0.22	0.13

SD: Standard deviation; GD: Gambling disorder; HC: Healthy controls; K_i: net influx rate; BP_{ND}: Binding potential.

Prior studies of cue-reactivity in GD have been heterogeneous in terms of methodology and produced mixed results (Balodis et al., 2012; Choi et al., 2012; Crockford et al., 2005; Kober H et al., 2016; Limbrick-Oldfield EH et al., 2017; Potenza et al., 2003; Sescousse, Barbalat, Domenech, & Dreher, 2013; van Holst, Veltman, Büchel, van den Brink, & Goudriaan, 2012). Our study used gambling-related videos, similar to what has been used to verify increased striatal cue-induced dopamine responses in SUDs (Volkow et al., 2006). In GD, there are three prior studies that have used gambling-related videos to study cue-reactivity with fMRI. Potenza et al. (2003) and Kober H et al. (2016) both compared gambling-related content against baseline conditions (gray screens) shown before and after the videos, and reported both increased and decreased BOLD responses in GD compared to healthy volunteers in several brain regions. Crockford et al. (2005) compared gambling-related videos to nature videos and also reported widespread increases in BOLD responses in several brain regions. Contrary to the findings of the present study, none of these studies reported increased BOLD responses specifically in the striatum. The findings from these prior studies seemingly contradict the observations in SUDs (Cousijn et al., 2013; Engelmann et al., 2012; Koob & Volkow, 2010; Sjoerds et al., 2014; Zhou et al., 2019). However, the previous cue-reactivity studies in GD have investigated the effects across the whole brain, but our approach of specifically assessing cue-induced responses in the striatum enabled us to increase statistical power to detect these changes, despite a relatively small sample size, which is a limitation shared by practically all GD functional neuroimaging studies. Another strength of our study was the inclusion of natural reward cues (erotic videos) to assess specificity of the findings to gambling-related cues. Including this control condition strengthens the validity of

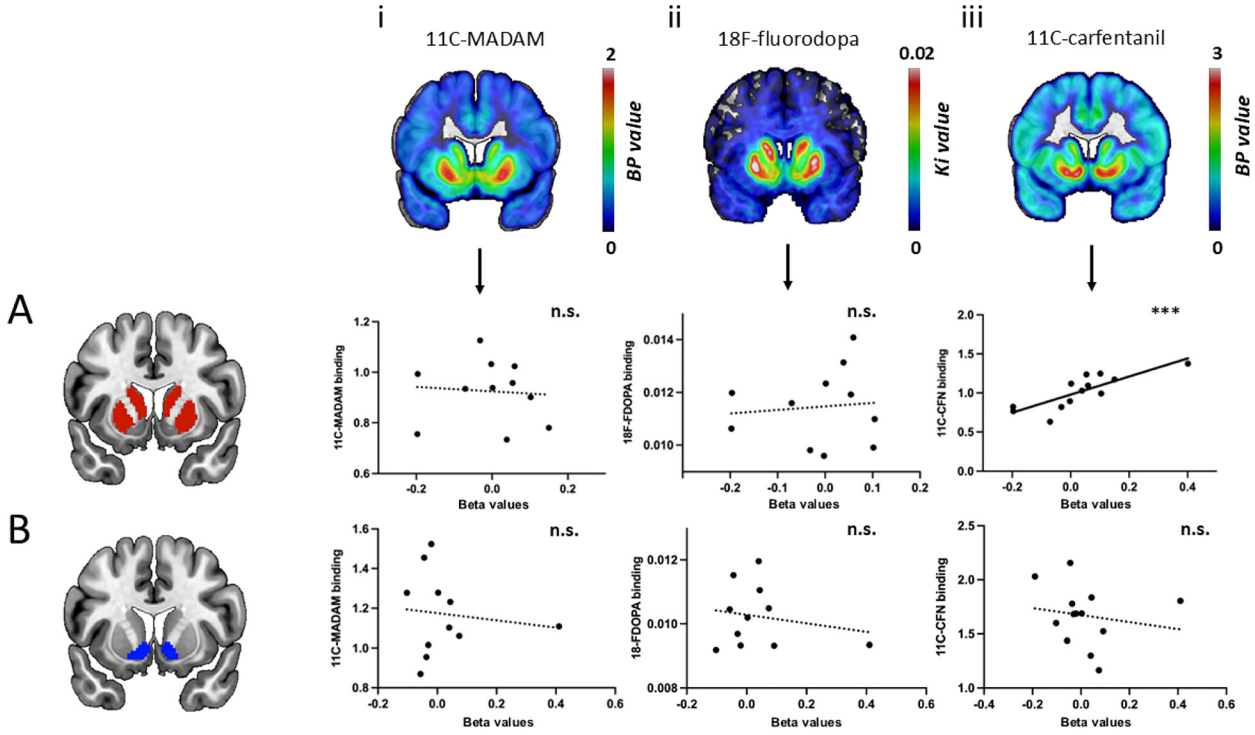

Fig. 4. **Correlation between cue-induced BOLD response and neurotransmitters.**
Dorsal (A) and ventral striatum (B) fMRI BOLD signal alongside dorsal and ventral striatum binding of [^{11}C]MADAM (serotonin transporter ligand) (i), [^{18}F]FDOPA (presynaptic dopamine synthesis capacity) (ii) and [^{11}C]carfentanil (mu-opioid receptors) (iii) in individuals with gambling disorder (GD). Note the significant correlation between [^{11}C]carfentanil BP_{ND} and fMRI BOLD signal in the dorsal striatum (difference between GD and HC correlation coefficients p = 0.001). The significance of the correlation did not change when excluding the subject with highest BP_{ND} and BOLD response.
n.s. = non significant. $^{***}p < 0.001$

our findings by reducing the likelihood that the observed striatal responses were simply due to a generalized sensitivity to cues associated with any rewarding stimuli.

We observed a coupling between the ventral and dorsal striatum BOLD response in HCs, but not in individuals with GD. This highlights a potential mechanism underlying impaired decision-making and reward processing in addiction. In HCs, the ventral striatum plays a crucial role in processing reward prediction and value, which is then passed to the dorsal striatum to guide action selection and habit formation (Everitt & Robbins, 2005). In GD, the decoupling between these regions could indicate a disruption in this process, where the the dorsal striatum may become overactive and more independent from the ventral striatum function, leading to compulsive gambling behaviors. This decoupling aligns with models of addiction hypothesizing a shift from ventral striatum-dominant (goal-directed) to dorsal striatum-dominant (habitual) behavior, driven by alterations in corticostriatal circuitry (Everitt & Robbins, 2005).

In this study, dorsal striatal BOLD response to gambling videos was associated with mu-opioid binding in this region. The association between dorsal striatum BOLD response to gambling-cues and mu opioid binding was significant in subjects with GD but not in HCs, suggesting specificity for GD. This finding aligns with the prior observations demonstrating an association between mu opioid receptor binding potential and craving in individuals with SUDs (Gorelick et al., 2005), a state commonly elicited in cue-reactivity paradigms (Antons, Brand, & Potenza, 2020; Kauer & Malenka, 2007). Accordingly, opioid antagonists have shown to reduce cue-induced responses and reward impulsivity, supporting the role of the opioid system in cue-reactivity and craving (Weber et al., 2016). In addition, naltrexone, an opioid antagonist, reduced cue-reactivity by enhancing the functional connectivity between the dorsal striatum and prefrontal regions during methamphetamine cue processing (Courtney, Ghahremani, and Ray (2016)).

In contrast to mu opioid receptor binding, we did not find an association between presynaptic dopamine synthesis capacity or serotonin transporter binding and striatal cue-induced BOLD responses. Prior research has demonstrated that cue-reactivity in SUDs is associated with striatal dopamine D2/D3 receptor binding (Volkow et al., 2006), but these findings may not generalize to behavioral addictions, as SUDs are associated with reduced striatal dopamine function, but GD is not (Boileau et al., 2013; Clark et al., 2012; Joutsa, Johansson, et al., 2012; Linnet et al., 2012; Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017). However, striatal dopaminergic function is modulated by the opioid system (Colasanti et al., 2012; Jalabert et al., 2011; Mick et al., 2014; Soderman & Unterwald, 2009; Tuominen et al., 2015) and both presynaptic dopamine synthesis capacity and dopamine D2/D3 receptor binding have been shown correlate with mu opioid receptor binding in the dorsal striatum (Colasanti et al., 2012; Majuri et al., 2018; Mick et al., 2014; Tuominen et al., 2015). Yet, dopamine is still likely to have a role in GD, as GD and other behavioral addictions (termed impulse control disorders in this context) are more common in Parkinson's disease patients on dopaminergic medications compared to general population (Joutsa, Martikainen, Vahlberg, Voon, & Kaasinen, 2012; Weintraub et al., 2010). Moreover, Parkinson's disease patients with impulse control disorders have been shown to have decreased mesolimbic dopamine synthesis capacity, transporter binding and postsynaptic D2/3 receptor binding compared to patients without impulse control disorders, contrasting the findings in GD in individuals without Parkinson's disease and dopaminergic medications (Cilia et al., 2010; Hammes et al., 2019; O'Sullivan et al., 2011; Steeves et al., 2009; Voon et al., 2014; Vriend et al., 2014; Wu et al., 2015). Thus, although striatal cue-reactivity does not directly correlate with striatal dopamine function in GD, cue-induced striatal responses may still be dopaminergic but abnormal cue-reactivity in GD is mediated via abnormalities of the opioid function. To our knowledge, this is the first neuroimaging study investigating neurotransmitter correlates of cue-reactivity in GD.

There are some limitations in the present study that should be considered when interpreting the results. First, as the sample size was low for an fMRI study, independent confirmation is warranted. However, the number of participants is comparable to the previous studies investigating cue-reactivity in GD. Second, it should be noted that while we found a significant group difference in hemodynamic responses to gambling videos (vs. neutral videos) within the dorsal striatum in the voxelwise analysis, this was not significant when using an anatomical ROI covering the entire dorsal striatum, likely reflecting the functional organization within the anatomical structure. Moreover, although this group difference was seen with gambling videos only, there was no significant group difference when contrasting gambling to erotic videos to further confirm the specificity to gambling cues. This contrasts with the previous study that reported blunted ventral striatal reactivity in pathological gamblers during the anticipation of erotic images vs. monetary cues (Sescousse, Caldú, et al., 2013). However, Sescousse et al. also did not find a group difference in striatal reactivity during viewing the erotic images, which may more closely align with stimulus used in the present study (erotic videos). Alternatively, the lack of significant group difference in our study could also be related with the limited power in these analyses due to the small sample size, or not selecting the GD group based on their preferred gambling types and matching the gambling videos content with them, which could have increased the response magnitudes to gambling videos in gamblers (Limbrick-Oldfield EH et al., 2017). Third, it should be noted that the correlation between mu-opioid binding and the BOLD response in the dorsal striatum was higher than the general test-retest reliability for task-based fMRI and, therefore, the strength of correlation should be interpreted with caution. Fourth, we only studied specific components of the opioid, dopamine and serotonin systems, and negative findings with any of these should not be considered to exclude any abnormalities in the corresponding neurotransmitter systems overall. Finally, the

cross-sectional design of the study limits the ability to establish causality, as the findings are correlational in nature.

In summary, this study underscores the involvement of the dorsal striatum and its association with the endogenous opioid system in processing gambling-related cues in individuals with GD. This knowledge may inform future therapeutic interventions targeting the opioid system to reduce cue-induced cravings and relapse in GD.

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REFERENCES

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596.

Antons, S., Brand, M., & Potenza, M. N. (2020). Neurobiology of cue-reactivity, craving, and inhibitory control in non-substance addictive behaviors. *Journal of the Neurological Sciences*, *415*, 116952. https://doi.org/10.1016/j.jns.2020.116952.

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis*, *12*(1), 26–41. https://doi.org/10.1016/j.media.2007.06.004.

Balodis, I. M., Kober, H., Worhunsky, P. D., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2012). Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. *Biological Psychiatry*, *71*(8), 749–757. https://doi.org/10.1016/j.biopsych.2012.01.006.

Barratt (1985). Impulsiveness subtraits: Arousal and information processing. *Motivation, Emotion and Personality*, *99*, 137–146.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the beck depression inventory-II*. San Antonio, TX: Psychological Corporation.

Bellmunt-Gil, A., Majuri, J., Arponen, E., Kaasinen, V., & Joutsa, J. (2023). Abnormal frontostriatal connectivity and serotonin function in gambling disorder: A preliminary exploratory study. *Journal of Behavioral Addictions*, *1*(aop). https://doi.org/10.1556/2006.2023.00037.

Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P. M., … Zack, M. (2013). The D2/3 dopamine receptor in pathological gambling: A positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C]raclopride. *Addiction*, *108*(5), 953–963. https://doi.org/10.1111/add.12066.

Boileau, I., Payer, D., Chugani, B., Lobo, D. S. S., Houle, S., Wilson, A. A., … Zack, M. (2014). In vivo evidence for greater amphetamine-induced dopamine release in pathological gambling: A positron emission tomography study with [11C]-(+)-PHNO. *Molecular Psychiatry*, *19*(12), Article 12. https://doi.org/10.1038/mp.2013.163.

Choi, J.-S., Shin, Y.-C., Jung, W. H., Jang, J. H., Kang, D.-H., Choi, C.-H., … Kwon, J. S. (2012). Altered brain activity during reward anticipation in pathological gambling and obsessive-compulsive disorder. *Plos One*, *7*(9), e45938. https://doi.org/10.1371/journal.pone.0045938.

Cilia, R., Ko, J. H., Cho, S. S., van Eimeren, T., Marotta, G., Pellecchia, G., … Strafella, A. P. (2010). Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiology of Disease*, *39*(1), 98–104. https://doi.org/10.1016/j.nbd.2010.03.013.

Clark, L. (2010). Decision-making during gambling: An integration of cognitive and psychobiological approaches. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *365*(1538), 319–330. https://doi.org/10.1098/rstb.2009.0147.

Clark, L., Stokes, P. R., Wu, K., Michalczuk, R., Benecke, A., Watson, B. J., … Lingford-Hughes, A. R. (2012). Striatal dopamine D2/D3 receptor binding in pathological gambling is correlated with mood-related impulsivity. *NeuroImage*, *63*(1), 40–46. https://doi.org/10.1016/j.neuroimage.2012.06.067.

Colasanti, A., Searle, G. E., Long, C. J., Hill, S. P., Reiley, R. R., Quelch, D., … Rabiner, E. A. (2012). Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. *Biological Psychiatry*, *72*(5), 371–377. https://doi.org/10.1016/j.biopsych.2012.01.027.

Courtney, K. E., Ghahremani, D. G., & Ray, L. A. (2016). The effects of pharmacological opioid blockade on neural measures of drug cue-reactivity in humans. *Neuropsychopharmacology*, *41*(12), 2872–2881. https://doi.org/10.1038/npp.2016.99.

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2013). Neural responses associated with cue-reactivity in frequent cannabis users. *Addiction*

Biology, *18*(3), 570–580. https://doi.org/10.1111/j.1369-1600.2011.00417.x.

Crockford, D. N., Goodyear, B., Edwards, J., Quickfall, J., & el-Guebaly, N. (2005). Cue-induced brain activity in pathological gamblers. *Biological Psychiatry*, *58*(10), 787–795.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395.

Diekhof, E. K., Kaps, L., Falkai, P., & Gruber, O. (2012). The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude – An activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. *Neuropsychologia*, *50*(7), 1252–1266. https://doi.org/10.1016/j.neuropsychologia.2012.02.007.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*, *113*(28), 7900–7905. https://doi.org/10.1073/pnas.1602413113.

Engelmann, J. M., Versace, F., Robinson, J. D., Minnix, J. A., Lam, C. Y., Cui, Y., … Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. *NeuroImage*, *60*(1), 252–262. https://doi.org/10.1016/j.neuroimage.2011.12.024.

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., … Gorgolewski, K. J. (2019). fMRIPrep: A robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. *Nature Neuroscience*, *8*(11), Article 11. https://doi.org/10.1038/nn1579.

Fauth-Bühler, M., Mann, K., & Potenza, M. N. (2017). Pathological gambling: A review of the neurobiological evidence relevant for its classification as an addictive disorder. *Addiction Biology*, *22*(4), 885–897. https://doi.org/10.1111/adb.12378.

Gago, B., Fuxe, K., Agnati, L., Peñafiel, A., De La Calle, A., & Rivera, A. (2007). Dopamine D4 receptor activation decreases the expression of μ-opioid receptors in the rat striatum. *Journal of Comparative Neurology*, *502*(3), 358–366. https://doi.org/10.1002/cne.21327.

García-Castro, J., Cancela, A., & Cárdaba, M. A. M. (2023). Neural cue-reactivity in pathological gambling as evidence for behavioral addiction: A systematic review. *Current Psychology*, *42*(32), 28026–28037. https://doi.org/10.1007/s12144-022-03915-0.

Gorelick, D. A., Kim, Y. K., Bencherif, B., Boyd, S. J., Nelson, R., Copersino, M., … Frost, J. J. (2005). Imaging brain Mu-Opioid receptors in abstinent cocaine users: Time course and relation to cocaine craving. *Biological Psychiatry*, *57*(12), 1573–1582. https://doi.org/10.1016/j.biopsych.2005.02.026.

Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2006). Neurocognitive functions in pathological gambling: A comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*, *101*(4), 534–547. https://doi.org/10.1111/j.1360-0443.2006.01380.x.

Hammes, J., Theis, H., Giehl, K., Hoenig, M. C., Greuel, A., Tittgemeyer, M., … van Eimeren, T. (2019). Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control. *Brain*, *142*(3), 733–743. https://doi.org/10.1093/brain/awz007.

Hnasko, T. S., Sotak, B. N., & Palmiter, R. D. (2005). Morphine reward in dopamine-deficient mice. *Nature*, *438*(7069), 854–857. https://doi.org/10.1038/nature04172.

Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: The role of reward-related learning and memory. *Annual Review of Neuroscience*, *29*, 565–598. https://doi.org/10.1146/annurev.neuro.29.051605.113009.

Jalabert, M., Bourdy, R., Courtin, J., Veinante, P., Manzoni, O. J., Barrot, M., & Georges, F. (2011). Neuronal circuits underlying acute morphine action on dopamine neurons. *Proceedings of the National Academy of Sciences*, *108*(39), 16446–16450. https://doi.org/10.1073/pnas.1105418108.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132.

Johansson, J., Keller, S., Tuisku, J., & Teräs, M. (2016). Performance of an image-based motion compensation algorithm for the hrrt: A striatum-phantom study with true motion. *IEEE Nuclear Science Symposium, Medical Imaging Conference and Room-Temperature Semiconductor Detector Workshop (NSS/MIC/RTSD)*, 1–3. https://doi.org/10.1109/NSSMIC.2016.8069586.

Joutsa, J., Johansson, J., Niemelä, S., Ollikainen, A., Hirvonen, M. M., Piepponen, P., … Kaasinen, V. (2012). Mesolimbic dopamine release is linked to symptom severity in pathological gambling. *NeuroImage*, *60*(4), 1992–1999. https://doi.org/10.1016/j.neuroimage.2012.02.006.

Joutsa, J., Martikainen, K., Vahlberg, T., Voon, V., & Kaasinen, V. (2012). Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism & Related Disorders*, *18*(2), 155–160. https://doi.org/10.1016/j.parkreldis.2011.09.007.

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nature Reviews Neuroscience*, *8*(11), 844–858. https://doi.org/10.1038/nrn2234.

Kober, H., Lacadie, C. M., Wexler, B. E., Malison, R. T., Sinha, R., & Potenza, M. N. (2016). Brain activity during cocaine craving and gambling urges: An fMRI study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *41*(2), 628–637. https://doi.org/10.1038/npp.2015.193.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*(1), 217–238.

Lesieur, H. R., & Blume, S. B. (1987). The South Oaks Gambling Screen (SOGS): A new instrument for the identification of pathological gamblers. *The American Journal of Psychiatry*, *144*(9), 1184–1188. https://doi.org/10.1176/ajp.144.9.1184.

Limbrick-Oldfield, E. H., Mick, I., Cocks, R. E., McGonigle, J., Sharman, S. P., Goldstone, A. P, … Clark, L. (2017). Neural substrates of cue reactivity and craving in gambling disorder. *Translational Psychiatry*, *7*(1), e992. https://doi.org/10.1038/tp.2016.256.

Linnet, J., Mouridsen, K., Peterson, E., Møller, A., Doudet, D. J., & Gjedde, A. (2012). Striatal dopamine release codes uncertainty in pathological gambling. *Psychiatry Research: Neuroimaging*, *204*(1), 55–60. https://doi.org/10.1016/j.pscychresns.2012.04.012.

Linnet, J., Peterson, E., Doudet, D. J., Gjedde, A., & Møller, A. (2010). Dopamine release in ventral striatum of pathological gamblers losing money. *Acta Psychiatrica Scandinavica*, *122*(4), 326–333. https://doi.org/10.1111/j.1600-0447.2010.01591.x.

Majuri, J., Joutsa, J., Arponen, E., Forsback, S., & Kaasinen, V. (2018). Dopamine synthesis capacity correlates with μ-opioid receptor availability in the human basal ganglia: A triple-tracer PET study. *NeuroImage*, *183*, 1–6. https://doi.org/10.1016/j.neuroimage.2018.07.069.

Majuri, J., Joutsa, J., Johansson, J., Voon, V., Alakurtti, K., Parkkola, R., … Kaasinen, V. (2017). Dopamine and opioid neurotransmission in behavioral addictions: A comparative PET study in pathological gambling and binge eating. *Neuropsychopharmacology*, *42*(5), Article 5. https://doi.org/10.1038/npp.2016.265.

Majuri, J., Joutsa, J., Johansson, J., Voon, V., Parkkola, R., Alho, H., … Kaasinen, V. (2017). Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [11C]MADAM. *European Neuropsychopharmacology*, *27*(12), 1281–1288. https://doi.org/10.1016/j.euroneuro.2017.09.007.

Mawlawi, O., Martinez, D., Slifstein, M., Broft, A., Chatterjee, R., Hwang, D. R., … Laruelle, M. (2001). Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *21*(9), 1034–1057. https://doi.org/10.1097/00004647-200109000-00002.

Mick, I., Myers, J., Stokes, P. R. A., Erritzoe, D., Colasanti, A., Bowden-Jones, H., … Lingford-Hughes, A. R. (2014). Amphetamine induced endogenous opioid release in the human brain detected with [11C]carfentanil PET: Replication in an independent cohort. *International Journal of Neuropsychopharmacology*, *17*(12), 2069–2074. https://doi.org/10.1017/S1461145714000704.

Nummenmaa, L., & Tuominen, L. (2018). Opioid system and human emotions. *British Journal of Pharmacology*, *175*(14), 2737–2749. https://doi.org/10.1111/bph.13812.

Oldham, S., Murawski, C., Fornito, A., Youssef, G., Yücel, M., & Lorenzetti, V. (2018). The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task. *Human Brain Mapping*, *39*(8), 3398–3418. https://doi.org/10.1002/hbm.24184.

O'Sullivan, S. S., Wu, K., Politis, M., Lawrence, A. D., Evans, A. H., Bose, S. K., … Piccini, P. (2011). Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain*, *134*(4), 969–978. https://doi.org/10.1093/brain/awr003.

Potenza, M. N., Steinberg, M. A., Skudlarski, P., Fulbright, R. K., Lacadie, C. M., Wilber, M. K., … Wexler, B. E. (2003). Gambling urges in pathological gambling: A functional magnetic resonance imaging study. *Archives of General Psychiatry*, *60*(8), 828–836. https://doi.org/10.1001/archpsyc.60.8.828.

Reuter, J., Raedler, T., Rose, M., Hand, I., Gläscher, J., & Büchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience*, *8*(2), 147–148. https://doi.org/10.1038/nn1378.

Sescousse, G., Barbalat, G., Domenech, P., & Dreher, J.-C. (2013). Imbalance in the sensitivity to different types of rewards in pathological gambling. *Brain*, *136*(8), 2527–2538. https://doi.org/10.1093/brain/awt126.

Sescousse, G., Caldú, X., Segura, B., & Dreher, J.-C. (2013). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *37*(4), 681–696. https://doi.org/10.1016/j.neubiorev.2013.02.002.

Shaffer, H. J., & Hall, M. N. (2001). Updating and refining prevalence estimates of disordered gambling behaviour in the United States and Canada. *Canadian Journal of Public Health*, *92*(3), 168–172. https://doi.org/10.1007/BF03404298.

Shaffer, H. J., Hall, M. N., & Vander Bilt, J. (1999). Estimating the prevalence of disordered gambling behavior in the United States and Canada: A research synthesis. *American Journal of Public Health*, *89*(9), 1369–1376. https://doi.org/10.2105/AJPH.89.9.1369.

Sjoerds, Z., Brink, W. van den, Beekman, A. T. F., Penninx, B. W. J. H., & Veltman, D. J. (2014). Cue reactivity is associated with duration and severity of alcohol dependence: An fMRI study. *Plos One*, *9*(1), e84560. https://doi.org/10.1371/journal.pone.0084560.

Soderman, A. R., & Unterwald, E. M. (2009). Cocaine-induced mu opioid receptor occupancy within the striatum is mediated by dopamine D2 receptors. *Brain Research*, *1296*, 63–71. https://doi.org/10.1016/j.brainres.2009.08.035.

Starcke, K., Antons, S., Trotzke, P., & Brand, M. (2018). Cue-reactivity in behavioral addictions: A meta-analysis and methodological considerations. https://doi.org/10.1556/2006.7.2018.39.

Steeves, T. D. L., Miyasaki, J., Zurowski, M., Lang, A. E., Pellecchia, G., Van Eimeren, T., … Strafella, A. P. (2009). Increased striatal dopamine release in Parkinsonian patients with pathological gambling: A [11C] raclopride PET study. *Brain*, *132*(5), 1376–1385. https://doi.org/10.1093/brain/awp054.

The MathWorks Inc. (2021). *MATLAB version: 9.11.0 (R2021b)*. Natick, Massachusetts: The MathWorks Inc. https://www.mathworks.com.

Tuominen, L., Tuulari, J., Karlsson, H., Hirvonen, J., Helin, S., Salminen, P., … Nummenmaa, L. (2015). Aberrant mesolimbic dopamine–opiate interaction in obesity. *NeuroImage*, *122*, 80–86. https://doi.org/10.1016/j.neuroimage.2015.08.001.

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 bias correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908.

Unterwald, E. M., & Cuntapay, M. (2000). Dopamine–opioid interactions in the rat striatum: A modulatory role for dopamine D1 receptors in delta opioid receptor-mediated signal transduction. *Neuropharmacology*, *39*(3), 372–381. https://doi.org/10.1016/S0028-3908(99)00154-9.

van Holst, R. J., Veltman, D. J., Büchel, C., van den Brink, W., & Goudriaan, A. E. (2012). Distorted expectancy coding in problem

gambling: Is the addictive in the anticipation? *Biological Psychiatry*, *71*(8), 741–748. https://doi.org/10.1016/j.biopsych.2011.12.030.

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Logan, J., Childress, A.-R., … Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: Mechanism of craving in cocaine addiction. *Journal of Neuroscience*, *26*(24), 6583–6588. https://doi.org/10.1523/JNEUROSCI.1544-06.2006.

Vollstädt-Klein, S., Wichert, S., Rabinstein, J., Bühler, M., Klein, O., Ende, G., … Mann, K. (2010). Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. *Addiction*, *105*(10), 1741–1749. https://doi.org/10.1111/j.1360-0443.2010.03022.x.

Voon, V., Rizos, A., Chakravartty, R., Mulholland, N., Robinson, S., Howell, N. A., … Ray Chaudhuri, K. (2014). Impulse control disorders in Parkinson's disease: Decreased striatal dopamine transporter levels. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(2), 148–152. https://doi.org/10.1136/jnnp-2013-305395.

Vriend, C., Nordbeck, A. H., Booij, J., van der Werf, Y. D., Pattij, T., Voorn, P., … van den Heuvel, O. A. (2014). Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *29*(7), 904–911. https://doi.org/10.1002/mds.25886.

Weber, S. C., Beck-Schimmer, B., Kajdi, M.-E., Müller, D., Tobler, P. N., & Quednow, B. B. (2016). Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans. *Translational Psychiatry*, *6*(7), e850–e850. https://doi.org/10.1038/tp.2016.113.

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., … Lang, A. E. (2010). Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients. *Archives of Neurology*, *67*(5), 589–595. https://doi.org/10.1001/archneurol.2010.65.

Welte, J. W., Barnes, G. M., Tidwell, M.-C. O., Hoffman, J. H., & Wieczorek, W. F. (2015). Gambling and problem gambling in the United States: Changes between 1999 and 2013. *Journal of Gambling Studies*, *31*(3), 695–715. https://doi.org/10.1007/s10899-014-9471-4.

Welte, J. W., Barnes, G. M., Wieczorek, W. F., Tidwell, M.-C., & Parker, J. (2002). Gambling participation in the U.S.—Results from a national survey. *Journal of Gambling Studies*, *18*(4), 313–337. https://doi.org/10.1023/A:1021019915591.

Wong, D. F., Kuwabara, H., Schretlen, D. J., Bonson, K. R., Zhou, Y., Nandi, A., … London, E. D. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology*, *31*(12), 2716–2727. https://doi.org/10.1038/sj.npp.1301194.

Wu, K., Politis, M., O'Sullivan, S. S., Lawrence, A. D., Warsi, S., Bose, S., … Piccini, P. (2015). Single versus multiple impulse control disorders in Parkinson's disease: An 11C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. *Journal of Neurology*, *262*(6), 1504–1514. https://doi.org/10.1007/s00415-015-7722-7.

Zald, D. H., Boileau, I., El-Dearedy, W., Gunn, R., McGlone, F., Dichter, G. S., & Dagher, A. (2004). Dopamine transmission in the human striatum during monetary reward tasks. *Journal of Neuroscience*, *24*(17), 4105–4112. https://doi.org/10.1523/JNEUROSCI.4643-03.2004.

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions of Medical Imaging*, *20*(1), 45–47. https://doi.org/10.1109/42.906424.

Zhou, X., Zimmermann, K., Xin, F., Zhao, W., Derckx, R. T., Sassmannshausen, A., … Becker, B. (2019). Cue reactivity in the ventral striatum characterizes heavy cannabis use, whereas reactivity in the dorsal striatum mediates dependent use. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(8), 751–762. https://doi.org/10.1016/j.bpsc.2019.04.006.

Appendix

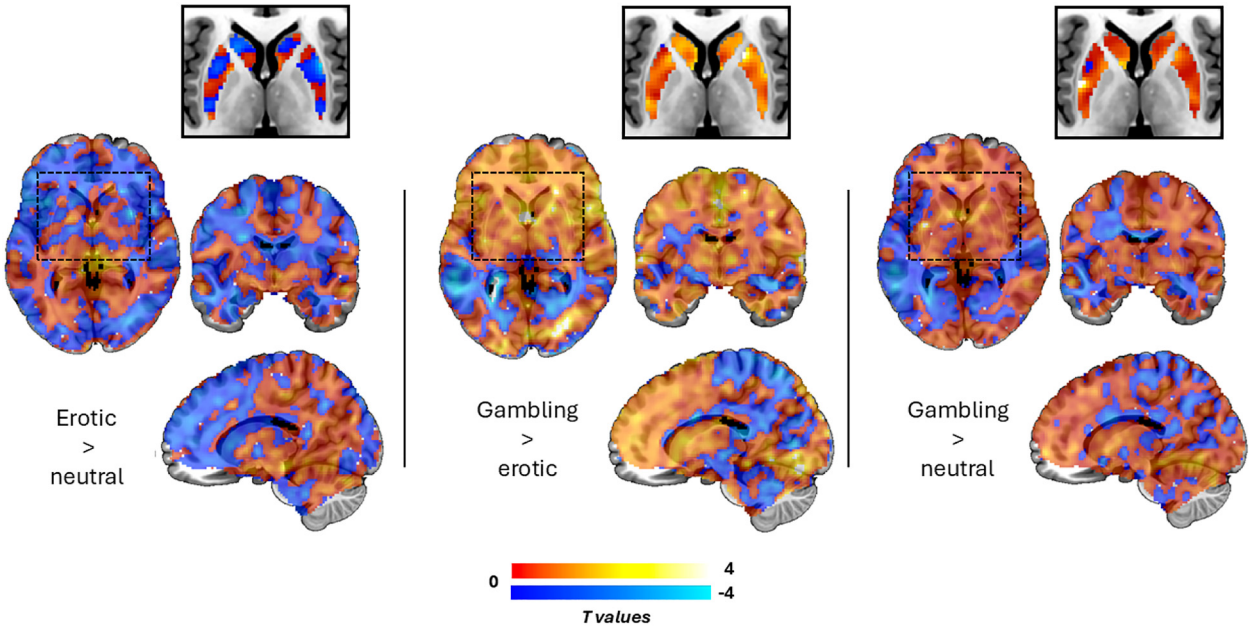

Fig. A1. Unthresholded whole-brain and striatum contrast maps gambling disorder (GD) > healthy controls (HCs)

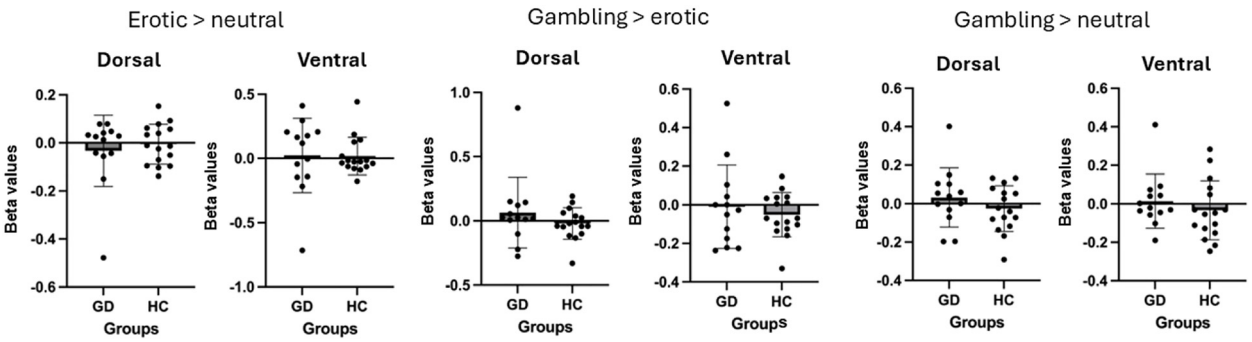

Fig. A2. **Hemodynamic responses for each group and condition extracted using anatomical regions-of-interest for the dorsal and ventral striatum.**

The regions-of-interest are shown in Fig. 4. None of the group differences were significant using the anatomical regions-of-interest. GD = gambling disorder. HC = Healthy controls