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FULL-LENGTH REPORT

Abnormal frontostriatal connectivity and serotonin function in gambling disorder: A preliminary exploratory study

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ABSTRACT

Background: The neurobiological mechanisms of gambling disorder are not yet fully characterized, limiting the development of treatments. Defects in frontostriatal connections have been shown to play a major role in substance use disorders, but data on behavioral addictions, such as gambling disorder, are scarce. The aim of this study was to 1) investigate whether gambling disorder is associated with abnormal frontostriatal connectivity and 2) characterize the key neurotransmitter systems underlying the connectivity abnormalities. *Methods:* Fifteen individuals with gambling disorder and 17 matched healthy controls were studied with resting-state functional connectivity MRI and three brain positron emission tomography scans, investigating dopamine (^{18}F-FDOPA), opioid (^{11}C-carfentanil) and serotonin (^{11}C-MADAM) function. Frontostriatal connectivity was investigated using striatal seed-to-voxel connectivity and compared between the groups. Neurotransmitter systems underlying the identified connectivity differences were investigated using region-of-interest and voxelwise approaches. *Results:* Individuals with gambling disorder showed loss of functional connectivity between the right nucleus accumbens (NAcc) and a region in the right dorsolateral prefrontal cortex (DLPFC) (P_{FWE} <0.05). Similarly, there was a significant Group x right NAcc interaction in right DLPFC ^{11}C-MADAM binding (p = 0.03) but not in ^{18}F-FDOPA uptake or ^{11}C-carfentanil binding. This was confirmed in voxelwise analyses showing a widespread Group x right NAcc interaction in the prefrontal cortex ^{11}C-MADAM binding (P_{FWE} <0.05). Right NAcc ^{11}C-MADAM binding potential correlated with attentional impulsivity in individuals with gambling disorder (r = −0.73, p = 0.005). *Discussion:* Gambling disorder is associated with right hemisphere abnormal frontostriatal connectivity and serotonergic function. These findings will contribute to understanding the neurobiological mechanism and may help identify potential treatment targets for gambling disorder.

KEYWORDS

gambling disorder, frontostriatal connectivity, NAcc, DLPFC, rs-fcMRI, PET, serotonin

INTRODUCTION

Gambling disorder (GD) affects 1–3.5% of the adult population (Shaffer, Hall, & Vander Bilt, 1999; Shaffer & Hall, 2001; Stevens, Dorstyn, Delfabbro, & King, 2021; Welte, Barnes, Wieczorek, Tidwell, & Parker, 2002) with similar estimates (0.3–4%) from Scandinavia (Bakken, Götestam, Gråwe, Wenzel, & Øren, 2009; Ekholm et al., 2014; Salonen, Hagfors, Lind, & Kontto, 2020; Volberg, Abbott, Rönnberg, & Munck, 2001). GD shares many core features of substance use disorders (SUDs), such as changes in reward processing,

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compulsion, withdrawal and lack of executive control (Koob & Volkow, 2010), and is considered a form of behavioral addiction (Potenza, 2008). The neurobiological mechanisms of GD, however, are not yet well characterized, and there are no established pharmacological or neuromodulation treatments for GD (Koob & Volkow, 2010).

The nucleus accumbens (NAcc), which is located in the ventral striatum, is one of the key structures in brain reward processing (Schultz, Dayan, & Montague, 1997). Rewarding stimuli lead to phasic increases in synaptic dopamine levels in the NAcc, signaling the magnitude of the reward and the prediction error (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). In substance use disorders, these responses are blunted, and there is a shift from ventral (rewards) to dorsal (cues, habits) striatal dopamine signaling, which is thought to underlie the transition from recreational to compulsive drug use (Koob & Volkow, 2010). However, although SUDs are characterized by abnormal dopamine signaling in the striatum (Volkow, Fowler, Wang, Baler, & Telang, 2009), pharmacotherapy targeting the dopamine system has been shown to be ineffective for the treatment of these disorders (Álvarez, Pérez-Mañá, Torrens, & Farré, 2013; Verrico, Haile, Newton, Kosten, & Garza, 2013). In addition, molecular imaging studies in GD have not aligned with the SUD findings, showing normal or even increased dopamine function (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017), suggesting that neurotransmitter systems other than dopamine may be relevant in GD.

Striatal dopamine signaling is modulated by other neurotransmitters, such as opioids and serotonin, and GD is associated with abnormalities in these neurotransmitter systems (Kaasinen et al., 2023; Majuri, Joutsa, Arponen, Forsback, & Kaasinen, 2018; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017). Drugs targeting the opioid and serotonin systems have shown some preliminary evidence for efficacy in the treatment of GD with the strongest data suggesting efficacy and tolerability of opioid antagonists but the results remain inconclusive (Black, Shaw, Forbush, & Allen, 2007; Bullock & Potenza, 2012; Dannon, Lowengrub, Gonopolski, Musin, & Kotler, 2005; Fong, Kalechstein, Bernhard, Rosenthal, & Rugle, 2008; Grant et al., 2006, 2014; Grant & Potenza, 2006; Hollander, Frenkel, Decaria, Trungold, & Stein, 1992, 2000; Kim, Grant, Adson, & Zaninelli, 2002; Petry & Armentano, 1999). The evidence for efficacy of the pharmacotherapies however is weaker compared to cognitive-behavioral therapy, which has shown moderate evidence for treatment of GD (Di Nicola et al., 2020).

Striatal function is modulated by the prefrontal cortex (Koob & Volkow, 2010), the frontostriatal circuits play a major role not only in reward processing but also in habit formation, decision-making and inhibitory control, which are all abnormal in GD (Alessi & Petry, 2003; Brevers & Noël, 2013; Verdejo-García, Lawrence, & Clark, 2008). The prefrontal cortex could be considered to act as "a brake" on the reward system, controlling our behavior over the urges (Aron, Robbins, & Poldrack, 2014; Bechara, 2005; Bechara & Van Der Linden, 2005). In the frontostriatal regions, GD is associated with abnormal cue reactivity in task-based fMRI studies (Balodis et al., 2012; Choi et al., 2012; Contreras-Rodríguez et al., 2016; de Greck et al., 2010; Fujimoto et al., 2017; Gelskov, Madsen, Ramsøy, & Siebner, 2016; Jung et al., 2014; Koehler et al., 2013; Miedl, Fehr, Meyer, & Herrmann, 2010; Sescousse, Barbalat, Domenech, & Dreher, 2013, 2016), several changes in neurotransmitter function (Boileau et al., 2014; Kaasinen et al., 2023; Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017; Pettorruso et al., 2019; van Holst et al., 2018) and possibly also structural abnormalities (Li et al., 2019; Yip et al., 2018; Zois et al., 2017). It should be noted however that addiction neurobiology is complex and involves changes in multiple neurotransmitter systems and circuits (Koob & Volkow, 2016; Uhl, Koob, & Cable, 2019; Yau & Potenza, 2015). Although frontostriatal function is considered to be important in addictive behaviors and it the focus of the present study, it is only one component of these disorders (Balodis et al., 2012; Choi et al., 2012; Contreras-Rodríguez et al., 2016; de Greck et al., 2010; Fujimoto et al., 2017; Gelskov et al., 2016; Jung et al., 2014; Koehler et al., 2013; Miedl et al., 2010, 2012; Sescousse et al., 2013, 2016).

Given the important role of the frontostriatal circuits, regions in the prefrontal cortex have been probed as a potential neuromodulation target using repetitive transcranial magnetic stimulation (rTMS) (Brevers, Noël, He, Melrose, & Bechara, 2016; Volkow et al., 2001, 2007). Several studies have investigated the efficacy of rTMS, both in GD (Pettorruso et al., 2021) and SUDs (Amiaz, Levy, Vainiger, Grunhaus, & Zangen, 2009; Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Mishra, Nizamie, Das, & Praharaj, 2010), but the results are variable, and the optimal target within the prefrontal cortex has remained elusive. Identifying the circuits and molecular abnormalities underlying GD is necessary to zero in on the most promising treatment targets using pharmacotherapy and noninvasive brain stimulation, such as rTMS.

In this study, we investigated frontostriatal connectivity and associated neurotransmitter abnormalities (dopamine, serotonin, opioid) in GD and their correlates with symptom severity and impulsivity. We hypothesized that GD is associated with abnormal limbic frontostriatal connectivity, which is linked with abnormal neurotransmitter function and impulsivity.

METHODS

Subjects

Thirty-two subjects participated in this study: 15 subjects with GD and 17 healthy controls (HCs) without any history of gambling problems. To our knowledge, this dataset is the first with PET imaging of three neurotransmitter systems in the same GD population. The PET imaging group comparisons between individuals with GD and HCs have been published earlier (Majuri, Joutsa, Johansson, Voon,

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

For the GD group, the inclusion criterion was current pathological gambling to the DSM-IV criteria, evaluated by a clinical interview. The study protocol was submitted for approval before DSM-5 was published and therefore used DSM-IV criteria for pathological gambling. However, all subjects in the GD group also fulfilled DSM-5 criteria for GD and therefore we use the current term GD. The data collection was conducted in 2013–2015. For the control group, the inclusion criteria were the absence of any gambling problems based on the clinical interview. For all subjects, the exclusion criteria included evidence for current clinically significant medical conditions, neurological disorders and other psychiatric disorders, evidence of current alcohol or substance use disorder, inability to pause medications affecting the central nervous system, body weight more than 180 kg (scanner limit), strong susceptibility to allergic reactions or nausea, current pregnancy, and any contraindications to magnetic resonance imaging.

Study protocol

The study included three visits. In the first visit, PG diagnosis was confirmed (GD group) or excluded (controls). The inclusion and exclusion criteria were evaluated at the first study visit by a licensed physician (J.M.) based on hospital records, clinical interview and clinical examination in consultation with the study senior investigators (J.J. and V.K.). Before PET imaging visit, laboratory tests including full blood cell count, liver function tests, blood glucose level, creatinine, urine drug screen and urine HCG test (for women) were obtained to ensure the subjects were eligible for PET imaging. The two study visits were conducted on separate days: 1) MR imaging and 2) all three PET scans. PET scans were performed at fixed intervals based on half-lives of radionuclides two allow for sufficient washout between the scans (11C tracers first and 18F-fluorodopa last). However, due to a scanner malfunction or tracer production failure, one [11C]carfentanil scan and two [18F]fluorodopa scans were performed on an additional separate study visit. The questionnaires (detailed in Clinical and behavioral measures) were filled out at the first visit and continued at the second visit if needed.

Before imaging, subjects were required to not have had a blood donation within 60 days, not drink alcohol for two days and not consume coffee or tea within the 12 h prior to imaging. Only one subject used a medication targeting the studied neurotransmitter systems. This subject with GD used citalopram for mild anxiety symptoms, which were in full remission at the time of the study. The subject was instructed to discontinue citalopram for at least five days before imaging and was excluded from the [11C]MADAM analysis. 2 other subjects (one with GD and one HC) because of excessive intra- and interframe head movement during scanning. Due to technical issues in scanning, one HC was not available for ^{11}C-carfentanil analysis, and one HC and two GD subjects were not available for the ^{18}F-FDOPA analysis (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017).

Clinical and behavioral measures

Clinical and behavioral information was collected during a clinical interview at the first study visit using validated questionnaires. Subject age, sex, body mass index (BMI) and smoking status were collected from all subjects. In addition, gambling-related information was collected, such as gambling hours per week, gambling euros per week and problematic gambling years. The questionnaires administered to all subjects included the South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987), Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Barratt Impulsiveness Scale (BIS-11) (Barratt, 1985) and the Alcohol Use Disorders Test (AUDIT) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993).

Image acquisition

All subjects underwent a brain MRI, including both structural and resting state functional MRI (rs-fMRI) scans, and three brain PET scans investigating serotonin (^{11}C-MADAM), dopamine (^{18}F-FDOPA) and opioid (^{11}C-carfentanil) neurotransmission.

MRI. 3D T1-weighted scans were obtained to provide a structural reference for the data analyses using a 3T PET-MRI scanner (Philips Ingenuity, Philips Healthcare, Cleveland, OH, USA) with a 34-channel receiving head coil. A sagittal 3DT1-weighted TFE sense pulse sequence (TR 8.1 ms, TE 3.7 ms, flip angle 7°, matrix 256 × 256, 176 slices) with isotropic voxels was obtained.

All participants underwent rs-fMRI scanning on a 3T PET-MRI scanner Philips Ingenuity (Philips Healthcare, Cleveland, OH, USA). The duration of the rs-fMRI scanning was 6 min with TR 2000 msec, TE 20 msec, flip angle 75°, 4 mm slice thickness, 35 slices, and parallel multislice mode. During scanning, the subjects were instructed to lie still with their eyes shut.

PET imaging. The PET imaging protocols have been described in detail earlier (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017). Briefly, PET imaging was performed using a high resolution research tomography (HRRT) PET scanner (Siemens Medical Solutions, Knoxville, TN, USA) with a nearly isotropic intrinsic spatial resolution of 2.5 mm (Jong et al., 2007). The scanning time was 51 min with ^{11}C-carfentanil, 90 min with ^{18}F-FDOPA and 90 min with ^{11}C-MADAM. 3D mode was used for the camera with scatter correction. PET scanning for all three tracers was performed during a single day at fixed intervals. Three subjects (one GD and two HC) underwent PET scans on two different days due to logistical issues. An individually shaped thermoplastic mask was used to reduce head movements during scanning, and head motion was recorded using a stereotaxic infrared camera (Polaris vicar, Northern Digital, Waterloo, Canada). Three GD patients used a Velcro strap instead of a thermoplastic mask because they felt the mask was uncomfortable.

Rs-fMRI data preprocessing and analyses

Rs-fMRI data processing was performed using the CONN Toolbox (version 19c, www.nitrc.org/projects/conn, RRID: SCR_009550). The preprocessing and denoising pipelines were created according to the CONN Toolbox documentation (https://web.conn-toolbox.org/fmri-methods) (Nieto-Castanon, 2020). Briefly, this included realignment, slice-timing correction, coregistration to the structural image, normalization to the MNI template, and spatial smoothing with an 8 mm full-width-half-maximum Gaussian kernel. The first four volumes of every subject's scan were excluded from the first-level analyses. After preprocessing, denoising was performed, including linear regression of potential confounding effects in the BOLD signal, which contained white matter and cerebrospinal fluid (10 dimensions for white matter and 5 for cerebrospinal fluid), estimated subject-motion parameters and identified outlier scans. Temporal bandpass filtering of 0.008 ~ 0.09 Hz was applied.

Striatal subregions from the CONN Toolbox were used as seeds in the connectivity analysis. The voxelwise analyses were restricted to the frontal cortex by creating an analysis mask using the MNI structural atlas from FSL (Collins, Holmes, Peters, & Evans, 1995; Mazziotta et al., 2001). To ensure that our results were not false-positives caused by the restricted search volume in the frontal cortex instead of the whole brain, the main result was confirmed using a whole-brain mask. The resulting connectivity values were z-transformed for the statistical analyses. Cluster-level familywise error (FWE) correction was used at height threshold $p < 0.001$ to avoid inflated false-positive rates associated with lower height thresholds with the fMRI data (Eklund, Nichols, & Knutsson, 2016). Corrected p values less than 0.05 were considered significant. Mean connectivity values were extracted from the significant clusters for illustration of the findings and subsequent correlation analyses with the PET imaging data.

PET imaging data preprocessing and analyses

PET imaging data preprocessing was performed as described earlier (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017). Briefly, realignment and coregistration of the images were performed with SPM8 software running on MATLAB R2012a (MathWorks, Natick, MA, USA). First, the individual PET images were realigned to correct any head movement during the PET scanning. The scan reconstruction has been described previously (Johansson, Keller, Tuisku, & Teräs, 2016). Regional data were extracted using regions of interest (ROIs) created by using recon-all with FreeSurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/) (Desikan et al., 2006; Fischl et al., 2002). These ROIs were used to extract the average time-activity courses for modeling. A Patlak plot was used to calculate the parametric ^{18}F-FDOPA K_i images, and a simplified reference tissue model was used to calculate ^{11}C-MADAM and ^{11}C-carfentanil BP_{ND} images. The cerebellar cortex was used as the reference region for ^{11}C-MADAM, and the occipital cortex for ^{18}F-FDOPA and ^{11}C-carfentanil (Gunn, Lammertsma, Hume, & Cunningham, 1997; Patlak & Blasberg, 1985). The parametric images were normalized to the Montreal Neurological Institute standard space (MNI152) using the spatial information from T1 s with DARTEL (Ashburner, 2007) and finally smoothed with a Gaussian kernel of 8 mm to improve the signal-to-noise ratio for statistical analyses. Two subjects differed significantly from the others (standard deviation >2) in their measurements from the right NAcc ^{11}C-MADAM BP_{ND}; therefore, they were considered outliers and excluded from the analyses concerning this variable.

First, to investigate neurotransmitters underlying the identified connectivity abnormality, BP_{ND}/K_i values were extracted from the significant connectivity cluster. A general linear model was created for each tracer separately using the cluster values as dependent variable testing for the Group x right NAcc interaction. Second, the results of the ROI analyses were confirmed in the corresponding voxelwise analyses implemented in SPM12, testing the Group x right NAcc interaction. The same frontal mask used for the connectivity analyses was used in the PET analyses. Cluster level familywise error (FWE) correction was used at height threshold $p < 0.005$, and FWE-corrected p values < 0.05 were considered significant, as described previously (Majuri, Joutsa, Johansson, Voon, Alakurtti, et al., 2017; Majuri, Joutsa, Johansson, Voon, Parkkola, et al., 2017).

Statistical analyses

Statistical analyses for ROI and clinical data were conducted using SPSS (IBM SPSS Statistics, version 27, Armonk, NY, USA). Independent samples t-tests and chi-square tests were used to test group differences in demographic and clinical data, as appropriate. Pearson and Spearman correlation coefficients were used to investigate the relationships between the clinical/behavioral and imaging data.

Ethics

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all subjects. This study was conducted according to the principles of the Declaration of Helsinki.

RESULTS

Demographics and clinical characteristics

The demographic and clinical characteristics of the studied subjects are presented in Table 1. There were no differences between the groups for age, sex, smoking or AUDIT score. As expected, GD subjects had significantly higher scores on gambling and impulsivity measures and the BDI than HCs (Table 1).

Table 1. Demographic and clinical characteristics

Variables (mean ± SD)	GD (n = 15)	HC (n = 17)	p value
Age (years)	42.6 ± 11.8	43.3 ± 11.1	0.87
Sex (male/female)	8/7	8/9	1.00
Gambling hours per week	8.9 ± 7.1	0.5 ± 1.2	<0.001
Gambling euros per week	164 ± 147	4 ± 7	<0.001
Problem gambling years	11.6 ± 7.3	0.00 ± 0.00	<0.001
PG DSM-IV points	7.3 ± 1.4	0.1 ± 0.3	<0.001
SOGS	13.3 ± 2.3	0.1 ± 0.3	<0.001
AUDIT	5.9 ± 4.0	5.4 ± 3.3	0.69
Smoking	11/4	7/10	0.07
BIS11_attention	19.2 ± 3.0	17.7 ± 1.9	0.09
BIS11_motor	26.5 ± 2.1	22.2 ± 2.4	<0.001
BIS11_nonplanning	28.5 ± 1.8	23.2 ± 4.5	<0.001
BDI	14.4 ± 7.8	2.8 ± 3.1	<0.001

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

Frontostriatal connectivity

GD patients had higher connectivity from the right NAcc (Fig. 1A) to the right dorsolateral prefrontal cortex (DLPFC) than controls (Fig. 1B). Specifically, the controls had negative connectivity (i.e., coupled but opposite changes in the BOLD signal) between these regions, which was lost in patients with GD (Fig. 1C). Controlling for age, sex, smoking or AUDIT did not change the significance of the results. In addition, repeating the analysis with a whole-brain mask instead of limiting it to the frontal cortex did not change the significance of the results. There were no significant connectivity differences from any other striatal ROIs to the frontal cortex (P_{FWE} >0.05).

The strength of NAcc-DLPFC connectivity did not correlate with the GD symptom severity or other gambling-related variables (p > 0.2). There was also no correlation between frontostriatal connectivity and BDI score (r = 0.22, p = 0.45) or AUDIT score (r = 0.20, p = 0.47).

Neurotransmitters

The average whole-brain maps for ^{11}C-MADAM, ^{18}F-FDOPA and ^{11}C-carfentanil BP_{ND} or K_i are shown in Fig. 2.

With ^{11}C-MADAM, there was a significant Group x right NAcc BP_{ND} interaction in the right DLPFC cluster (shown in Fig. 1B) for BP_{ND} (Fig. 3A, B) (F = 5.63, p = 0.03). This finding was confirmed in the voxelwise analysis, showing a Group x right NAcc BP_{ND} interaction in the prefrontal cortex (Fig. 3C), overlapping with the connectivity difference cluster (Fig. 4). There were no significant Group x right NAcc interactions with ^{18}F-FDOPA or ^{11}C-carfentanil. The right NAcc ROI ^{11}C-MADAM BP_{ND}, ^{18}F-FDOPA K_i and ^{11}C-carfentanil BP_{ND} did not differ significantly between the groups.

In individuals with GD, there was a significant correlation between the right NAcc MADAM BP_{ND} and attentional impulsivity (r = −0.73, p = 0.005). The right NAcc MADAM BP_{ND} correlation with gambling hours per week (r = 0.54, p = 0.06) and other variables, including BIS total score, BDI, AUDIT, smoking, or gambling-related variables, were not significant (p > 0.05).

DISCUSSION

The present study aimed to investigate the frontostriatal connectivity and associated neurotransmitter abnormalities

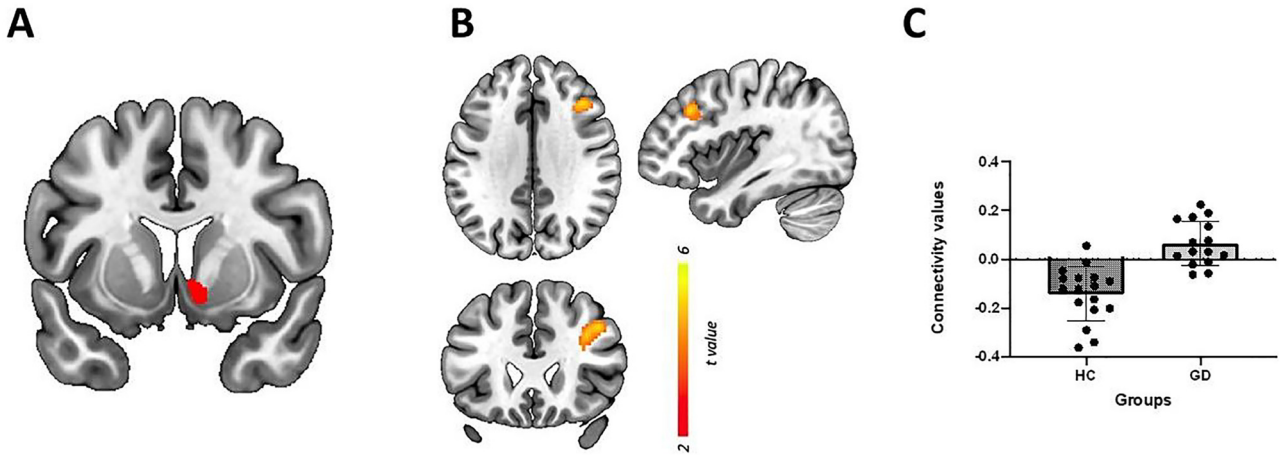

Fig. 1. Connectivity difference between individuals with GD and controls. A) Right nucleus accumbens region of interest (ROI) used as a seed for the resting state functional connectivity MRI analysis. B) Voxels showing significant Group x ROI connectivity differences in the right dorsolateral prefrontal cortex (DLPFC) (peak coordinates at 40 26 36, cluster size 187 voxels, P_{FWE} = 0.01). C) Group mean (SD) NAcc-DLPFC connectivity values [healthy controls (HC) −0.14(0.11) vs. individuals with GD (GD) 0.065(0.093), 95% CI [0.13, 0.28]]. Note that the values obtained from the significant cluster are used to illustrate the magnitude of the group difference and variance, not for statistical testing of the hypothesis, as this analysis would be circular

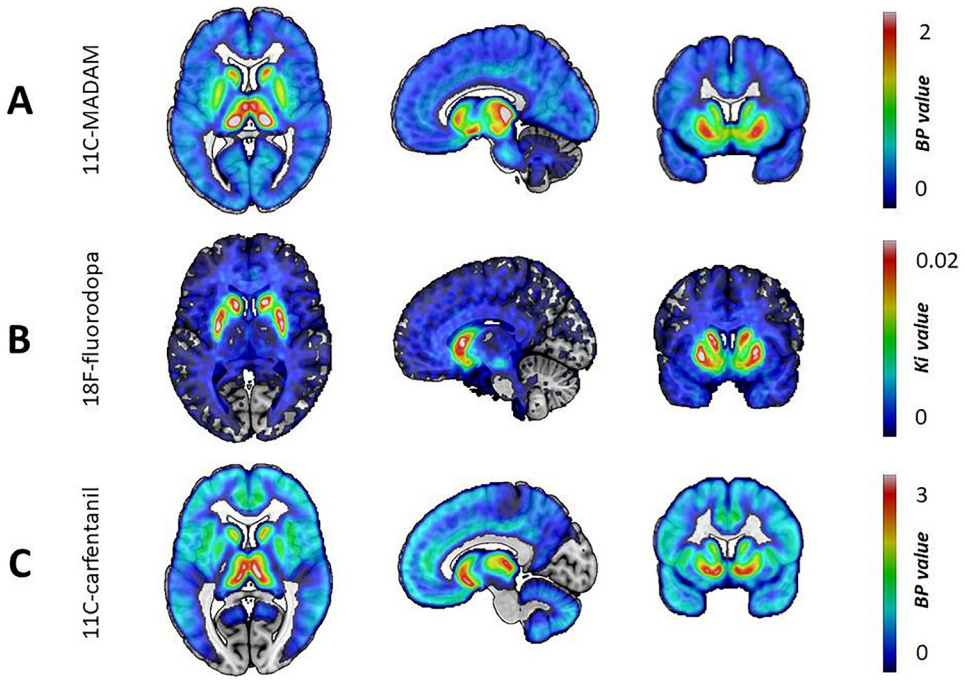

Fig. 2. Average voxelwise whole-brain maps for each tracer. Mean voxelwise whole-brain map for 11C-MADAM (serotonin transporter ligand) (A), ^{18}F-FDOPA (presynaptic dopamine synthesis capacity) (B) and ^{11}C-carfentanil (mu-opioid receptors) (C)

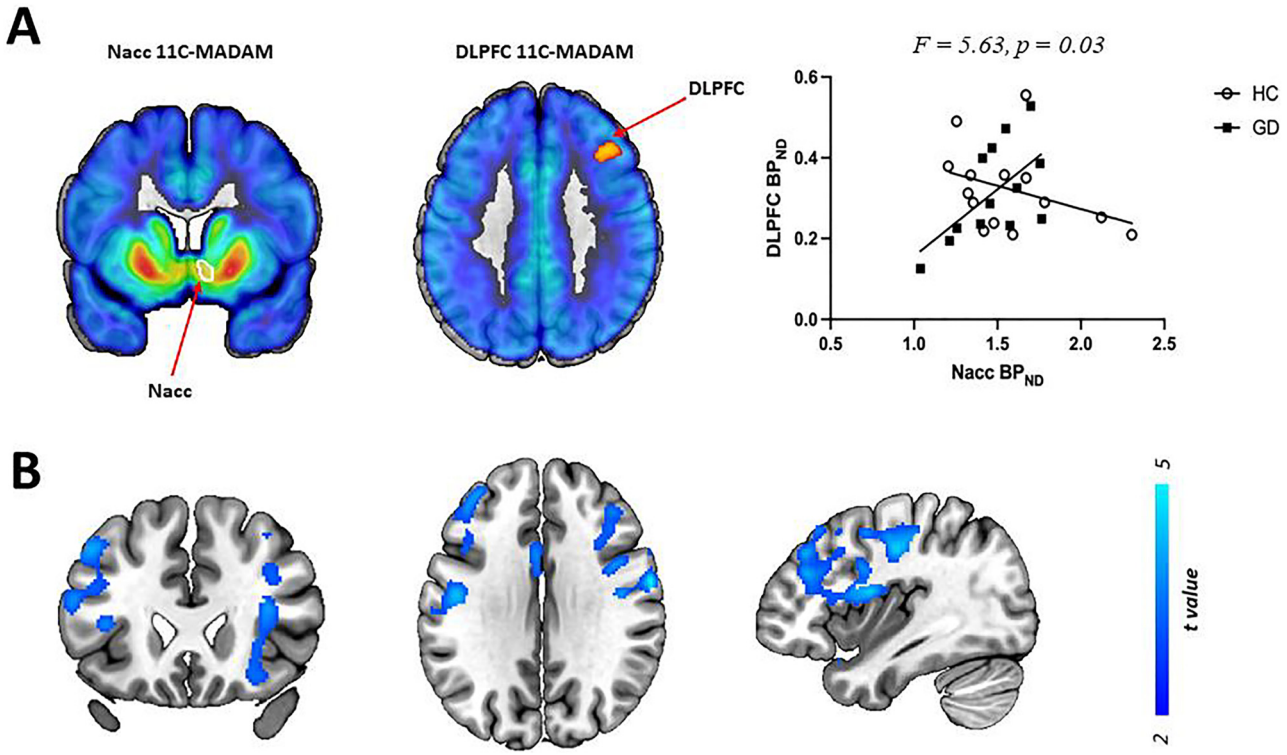

Fig. 3. Group x right NAcc interaction in MADAM BP_{ND}. A) Right nucleus accumbens (NAcc) and dorsolateral prefrontal cortex (DLPFC) regions of interest used to extract individual ^{11}C-MADAM BP_{ND} overlaid on the average ^{11}C-MADAM BP_{ND} demonstrating significant group x NAcc BP_{ND} interaction in the DLPFC BP_{ND}. B) Significant Group x right NAcc interaction (cluster peak at 62-6 40, size 7227 voxels, $P_{FWE} <$ 0.001; -48-28 38, 7844 voxels, $P_{FWE} <$ 0.001; -9-3 63, 2051 voxels, $P_{FWE} =$ 0.02

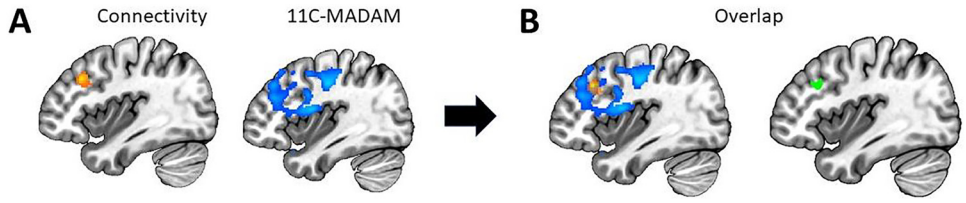

Fig. 4. Overlap between the DLPFC connectivity cluster and the Group x right NAcc interaction in MADAM BP_{ND}. Significant connectivity cluster and MADAM BP_{ND} right DLPFC clusters (A), overlapping at the right DLPFC (center of gravity coordinates at MNI coordinate 36 24 32)

in GD, and their correlates with symptom severity and impulsivity. The results of the present study demonstrate abnormal frontostriatal connectivity in GD. Specifically, GD was associated with loss of negative connectivity between the right nucleus accumbens and the right DLPFC. This connectivity abnormality was associated with brain serotonin but not opioid or dopamine function.

The nucleus accumbens is the projection site of the mesolimbic dopamine pathway, where rewards lead to phasic dopamine release, which is associated with a subjective feeling of pleasure (Joutsa et al., 2012; Koob & Volkow, 2010). These reward signals reinforce behavior and are considered critical for the development of addiction disorders (Volkow & Morales, 2015). Prefrontal cortex functions include decision-making, cognitive control and impulse inhibition and could be considered to act as "a brake" on the reward system, controlling our behavior over the urges (Aron et al., 2014; Bechara, 2005; Bechara & Van Der Linden, 2005). Prior studies have repeatedly demonstrated a clear loss of prefrontal control and abnormal frontostriatal function in SUDs (Ersche et al., 2012; Everitt, 2014; Hu, Salmeron, Gu, Stein, & Yang, 2015; Koob & Volkow, 2010; Morein-Zamir & Robbins, 2015). The findings of this study show that GD, a form of behavioral addiction, is also associated with a loss of normal frontostriatal connectivity, which is driven by serotonin function.

There is one previous study that reported NAcc-DLPFC connectivity dysfunction in GD (Koehler et al., 2013). In that study, Koehler et al. (2013) identified a region in the right DLPFC showing a gray matter volume increase, and this region was shown to have abnormal connectivity to subcortical regions, including the striatum. This finding aligns with our results in demonstrating abnormal connectivity from the right nucleus accumbens to the right DLPFC (Koehler et al., 2013). Loss of normal frontostriatal connectivity is also associated with impulsivity, which is one of the hallmarks of addiction disorders and is known to increase the risk for relapse after quitting (Courtney, Ghahremani, & Ray, 2013; Koob & Volkow, 2010; Morein-Zamir & Robbins, 2015; Wang et al., 2013). Thus, a growing body of evidence supports a role for prefrontal connections in GD, motivating treatment interventions, such as noninvasive brain stimulation, targeting this circuit (Pettorruso et al., 2021).

Likely motivated by the major success in the treatment of depression using rTMS, the left DLPFC has also been the most commonly used target for the treatment of GD. However, the results from these studies are mixed (Pettorruso et al., 2021). To date, only two rTMS studies have targeted the right DLPFC, both using inhibitory protocols (one with 1 Hz rTMS and one with cTBS), leading to reduced gambling reinforcement and suppression of the urge to gamble (Sauvaget et al., 2018; Zack et al., 2016). Combined with our findings, inhibitory stimulation of the right DLPFC may be a potential treatment strategy for GD, warranting further investigation. Targeting the right DLPFC also receives some support from the SUD literature, where rTMS has been shown to reduce craving in alcohol and cocaine dependence (Camprodon et al., 2007; Mishra et al., 2010).

Although the dopamine system is critical for the development of addiction disorders, the results from treatment trials using medications targeting the dopamine system have been disappointing (Fong et al., 2008; McElroy, Nelson, Welge, Kaehler, & Keck, 2008). Similarly, the evidence for the efficacy of opioid antagonist has been variable but so far opioid antagonists have seemed more effective than SSRIs (Bullock & Potenza, 2012; Victorri-Vigneau et al., 2018). However, it should be noted that later RCTs have failed to confirm the efficacy of opioid antagonists for treatment of GD (Alho et al., 2022; Kovanen et al., 2016). Although the data regarding serotonergic medications are far from conclusive, selective serotonin reuptake inhibitors (SSRIs) have been suggested to decrease impulsivity, urge to gamble and gambling frequency (Black et al., 2007; Dannon et al., 2005; Fong et al., 2008; Grant & Potenza, 2006; Hollander et al., 2000; Kim et al., 2002). However, due to lack of sufficient evidence, SSRIs currently are only recommended for GD with bipolar spectrum disorders (Bullock & Potenza, 2012).

Our findings suggest that the frontostriatal connectivity, associated with abnormal serotonin function, is involved in GD. However, as SSRIs have not shown convincing evidence for treatment of GD, drugs targeting other neurotransmitter systems may be more relevant for treatment and our study only investigated *resting* serotonin function. It is possible that other neurotransmitter systems, such as the opioid system, are driving gambling activity (Bullock & Potenza, 2012; Kraus, Etuk, & Potenza, 2020) and modifying these systems may be more relevant for controlling the pathological behavior. Thus, as frontostriatal dysconnectivity is mediated via serotonin, we can speculate that these medications could, at least partly, act by restoring frontostriatal

connections. However, this hypothesis needs to be empirically tested.

There are some limitations in the present study that should be considered when interpreting the results. First, although the number of subjects was comparable to the previous studies in the field, the sample size is low for a rs-fcMRI study. However, the observed connectivity difference was robust to different analysis strategies, and the results aligned well with prior observations, adding confidence to the findings. Nevertheless, our findings should still be considered preliminary, pending confirmation in an independent study. In addition, we did not find a relationship between the neural correlates and the clinical variables related to GD symptom severity, which could be related to the low sample size. Second, our study is the first to combine connectivity measures with PET imaging using multiple ligands but we are still limited by the fact that the present study was cross-sectional, preventing the establishment of causal relationships. Third, as ^{18}F-FDOPA and ^{11}C-carfentanil measure only one aspect of the dopamine and opioid systems, lack of significant findings with these tracers cannot be considered to exclude the possibility of frontostriatal connectivity abnormalities in these neurotransmitter systems. Finally, as serotonin transporter imaging does not directly reflect synaptic serotonin concentrations, the direction of the abnormal serotonin function remains speculative.

CONCLUSION

In summary, the results of the present study show that GD is associated with abnormalities in frontostriatal connectivity and resting-state serotonin function. These findings provide novel information about the neurobiological mechanisms underlying GD and may have relevance for treatment, highlighting the right DLPFC and serotonin system as possible testable treatment targets.

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SUPPLEMENTARY DATA

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