Striatal presynaptic dopaminergic dysfunction in gambling disorder: a ^{123}I-FP-CIT SPECT study

Mauro Pettorruso[1,*], M.D.; Giovanni Martinotti[2], M.D., PhD; Fabrizio Cocciolillo[3], M.D.; Luisa De Risio[1], M.D.; Annarita Cinquino[3], M.D.; Marco Di Nicola[1], M.D., PhD; Giovanni Camardese[1], M.D.; Giuseppe Migliara[4], M.D.; Lorenzo Moccia[1], M.D.; Eliana Conte[1], M.D.; Luigi Janiri[1,+], M.D.; Daniela Di Giuda[3,+], M.D.

[+] Shared last-author

[1] Institute of Psychiatry and Psychology, Fondazione Policlinico Universitario "A. Gemelli" Università Cattolica del Sacro Cuore, Rome, Italy.

[2] Department of Neuroscience Imaging and Clinical Science, ''G. d'Annunzio'' University of Chieti, Italy; Department of Pharmacy, Pharmacology and Clinical Science, University of Hertfordshire, Herts, UK.

[3] Institute of Nuclear Medicine, Fondazione Policlinico Universitario "A. Gemelli" Università Cattolica del Sacro Cuore, Rome, Italy.

[4] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy.

* Corresponding author:

Mauro Pettorruso, M.D.

Institute of Psychiatry and Psychology

Largo Agostino Gemelli, 8 – 00168 Roma

Tel. +39 06 30157275 - Email: mauro.pettorruso@hotmail.it

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Abstract

BACKGROUND: Although the involvement of dopamine in gambling disorder (GD) has long been hypothesized, its precise role remains unclear. The action of dopamine in the synapses is regulated by the dopamine transporter (DAT). We hereinafter present significant differences between a sample of 15 treatment-seeking GD subjects and 17 healthy controls in terms of striatal DAT availability, and we explore its association with reward-based decision making.

METHODS: We performed ^{123}I-FP-CIT SPECT and correlated DAT binding ratios in the bilateral caudate and putamen with gambling symptoms (G-SAS, PG-YBOCS) and behaviors, as well as other psychometric variables (anhedonia, impulsivity). GD subjects were also administered a computerized version of the Iowa Gambling Task (IGT) to assess reward-based decision-making.

RESULTS: We found reduced DAT availability in GD subjects compared to healthy controls (-13.30% in right caudate, -11.11% in right putamen, -11.44% in left caudate and -11.46% in the left putamen). We also found that striatal DAT availability was inversely correlated with days spent gambling and IGT performance in GD subjects.

CONCLUSIONS: These results provide evidence for a presynaptic dopaminergic dysfunction in striatal regions of GD subjects. Functional DAT down-regulation possibly sustains the transition towards compulsive gambling addiction, characterized both by hyper- and hypo-dopaminergic states in the context of a sensitized dopaminergic system.

1. Introduction

Gambling Disorder (GD) is characterized by persistent and maladaptive gambling behavior, despite serious adverse consequences. GD is a major public health concern, with a worldwide prevalence estimated between 0.2–5.3% . To date, GD pathophysiology is largely unknown. It is, therefore, urgent to further our understanding of its neurobiological underpinnings, in order to pave the way towards new treatment scenarios.

Alterations in dopaminergic pathways have been extensively hypothesized in GD (Linnet, 2014; Potenza, 2013), based on specific genetic polymorphism data (D2-D3 receptors; (Lobo et al., 2015) and epigenetic data (Angelucci et al., 2013), as well as new onset dopamine agonist-related behavioral addictions in Parkinson's Disease (PD) (Pettorruso et al., 2014b). It is still unclear whether GD is a hypodopaminergic (Luijten et al., 2017) or hyperdopaminergic condition (Boileau et al., 2014; van Holst et al., 2017), or both.

The dopamine transporter (DAT) has a pivotal role in regulating dopamine transmission (Vaughan and Foster, 2013). Besides reflecting the integrity of dopaminergic neurons projecting to the striatum, DAT terminates dopamine signaling at the synapse through high affinity reuptake of dopamine into presynaptic terminals, thereby controlling the spatial and temporal dynamics of dopaminergic neurotransmission (Rice and Cragg, 2008). DAT dysregulation, resulting in aberrant dopamine clearance, has long been suggested to result in dopaminergic dysfunction , as well as having a role in the pathophysiology of substance addictions (Addolorato et al., 2017; Ashok et al., 2017).

Brain imaging techniques have allowed neuroscientists to map out the neural landscape of GD and explore how different stimuli modify it. Growing evidence implicates a failure in top-down inhibitory prefrontal cortex (PFC) control over striatal outflow (Moccia et al., 2017). The altered interaction between prefrontal structures and the mesolimbic reward system in GD shares similarities with the functional organization reported in substance addiction, suggesting a more general pathophysiology for addictive disorders (Fauth-Buhler et al., 2017).

Neuropsychological studies have implicated the dopaminergic system and the PFC in mediating reward-based learning and decision-making. The Iowa Gambling Task (IGT) (Bechara et al., 1994) is considered an ecologically valid and reliable measure of reward-based decision-making and impaired IGT performances have been consistently associated with GD (Brevers et al., 2013) .

The aims of the present study were 1) to investigate striatal DAT availability in a sample of treatment-seeking GD patients and matched healthy controls (HC), using ^{123}I-FP-CIT SPECT; 2) to assess the impact of DAT availability on reward-based decision-making, as measured by the IGT; 3) to highlight possible correlations between DAT availability and gambling symptoms and behavior.

2. Methods

Fifteen treatment seeking, drug-free gamblers (14 males, 1 female) were recruited at the Addiction Unit of the Day Hospital of Psychiatry of the Fondazione Policlinico Universitario A. Gemelli (Catholic University of the Sacred Heart) in Rome. Participants were included in the study if they were 18-65 years old. They met DSM-5 criteria for GD, with a maximum of two months elapsing since last gambling session. Axis I and Axis II comorbidities were assessed (SCID-I and SCID II, respectively). Exclusion criteria were: medication interfering with DAT binding (Booij and Kemp, 2008); mental retardation or documented IQ $\leq$ 70; significant or unstable medical and/or neurological conditions; comorbid psychiatric disorders (i.e. schizophrenia, bipolar disorder, major depressive disorder); Hamilton Depression Rating Scale (HDRS) score $\geq$18 ; suicidal ideation; current or past alcohol and/or substance abuse; females of childbearing age not using acceptable birth control.

After screening to assess the eligibility and collect general clinical and sociodemographic data (visit 1), all subjects were administered the IGT and psychometric testing and underwent SPECT examination (visit 2; after 8.73±7.62 days).

Psychometric and SPECT results were compared with data from 17 matched HC (homogeneous with respect to age, gender, smoking status, level of education and ethnicity), retrieved from a previously collected SPECT database. All HC had been screened for addictive disorders. We included 17 HC to obtain the best matching for age, gender, smoking status, level of education and ethnicity.

The study was conducted in accordance with the declaration of Helsinki and with good clinical practice guidelines, and was approved by the local ethical committee (released in June 2013). All patients gave their written informed consent, after a complete description of the study was provided.

2.1 Psychometric assessment

The following tests were administered:

- the Yale-Brown Obsessive Compulsive Scale modified for GD (PG-YBOCS) ;
- the Gambling Severity Assessment Scale (G-SAS) ;
- the Timeline Follow Back (TLFB) for GD (to track gambling frequency, time spent gambling and money wagered) ;
- the HDRS, the Hamilton Anxiety Rating Scale (HARS) and the Young Mania Rating Scale (YMRS) to assess mood and anxiety symptoms;
- the Snaith-Hamilton Pleasure Scale (SHAPS;), a 14-item self-rating scale exploring hedonic responses in common pleasurable situations related to natural rewards (a total score > 2 indicates the occurrence of anhedonia);
- the 'anhedonia/asociality' subscale of the Scale for the Assessment of Negative Symptoms (SANS;);
- the 10 cm visual analogue scale (VAS;) for hedonic capacity;
- the Barratt Impulsiveness Scale (BIS-11;), a 30-item self-rating scale measuring trait impulsivity.

2.2 Iowa Gambling Task (IGT)

All participants were administered a computerized version of the IGT (Bechara et al., 1994). Subjects were provided with $2000 to start with. The computer screen displayed four rectangles (decks). Participants were instructed to select a card by clicking on the appropriate deck. Turning each card carries an immediate reward ($100 in decks A and B and $50 in decks C and D). Unpredictably, however, the turning of some cards also carries a penalty (which is large in decks A and B and small in decks C and D). Playing mostly from decks A and B leads to an overall loss. Playing from decks C and D leads to an overall gain. A key feature for optimal performance is that participants have to forego short-term benefit for long-term profit. The task ends after 100 card selections.

The NET score quantifies the amount of advantageous decision-making, calculated as the number of draws from advantageous decks minus that from disadvantageous decks: NET score = (selected cards Deck C + selected cards Deck D) - (selected cards Deck A + selected cards Deck B) .

NET scores typically vary across trials, which are accordingly separated into 5 blocks of 20 trials, with a NET score being calculated for each block. As a measure of reward-based decision-making, we therefore calculated the scores over the last three blocks (NET3-5; choices 41 to 100) .

2.3 SPECT imaging

SPECT acquisition and processing for GD subjects and HC were performed as previously published (Addolorato et al., 2017). According to current neuroimaging guidelines (Darcourt et al., 2010), 185 MBq of ^{123}I-FP-CIT (DaTSCAN™, G.E. Healthcare, United Kingdom) were administered intravenously 30 minutes after thyroid blockade (400 mg of oral potassium perchlorate).

SPECT was carried out using a dual-head gamma camera system (E.CAM; Siemens Medical Systems, Germany) equipped with high-resolution low-energy, parallel hole collimators. Acquisition started 180 minutes after radiotracer injection and lasted 45 minutes. A “step-and-shoot” protocol was applied with a 15% energy window centered on 159 KeV and the following

acquisition parameters: radius of rotation ≤ 15 cm, 20 projection angles over 360° (angular step of 3°), 128x128 matrix, zoom factor 1.23, pixel size 3.90x3.90 mm, 45 seconds per view. Data were reconstructed by filtered back-projection using a Butterworth filter (cut-off frequency: 0.45 cycle/cm, order 8). Chang's first order attenuation correction (correction coefficient: 0.11 cm^{-1}) was also performed, after manually drawing an ellipse around the head contour. Reconstructed transaxial, sagittal and coronal slices (slice thickness: 3.90 mm) were reoriented according to the plane connecting the frontal and occipital poles. All data were collected and analyzed by two experienced operators (D.D.G. and F.C.) blind to all clinical information. After a visual analysis of SPECT images, a semi-quantitative assessment was carried out using Statistical Parametric Mapping 8 (SPM8) (Wellcome Department of Cognitive Neurology, University College London, United Kingdom) under the Matlab 8.0 version (The MathWorks, Inc., Natick, MA, USA) in order to spatially normalize data. Moreover, the MarsBaR toolbox (version 0.43) (Brett et al., 2002) was employed to obtain a volume of interest (VOI) analysis within the SPM. As the use of SPM for DAT images requires a dedicated template, we generated our own template with the normal parametric images of the 17 HC according to the method suggested by Kas et al. (Kas et al., 2007). The normalization algorithm provided by SPM8 was employed to register ^{123}I-FP-CIT images with the template using default settings.

A correction for partial volume effect (PVE) was achieved importing all normalized images in the PMOD version 3.6 (PMOD Technologies Ltd, Zürich, Switzerland).

The ^{123}I-FP-CIT binding was assessed as the ratio between the specific and non-specific activity measured through VOIs placed over the right and left caudate and putamen (as radiotracer specific binding), as well as over the occipital cortex (as non-specific binding) of the normalized images. Indeed, at equilibrium of radiotracer distribution, this ratio corresponds to the distribution volume ratio, which is directly linked to the tracer binding potential in the target region (Acton et al., 2000; Innis et al., 2007). In particular, the VOIs were selected from the digital atlas resulting from an automatic anatomical segmentation of the spatially normalized, single subject, high resolution T1

Magnetic Resonance Imaging (MRI) data set provided by the Montreal Neurological Institute, MNI (Tzourio-Mazoyer et al., 2002). Lastly, using the MarSbaR toolbox, the mean counts per pixel were extracted from each VOI for all normalized PVE-corrected images. Specific to non-specific ^{123}I-FP-CIT binding ratio (SBR) was calculated in the putamen and caudate nucleus for the right and left hemispheres, employing the following formula: [(mean counts in striatal VOI)-(mean counts in occipital VOI)]/ (mean counts in occipital VOI).

In addition, an SPM analysis was performed to confirm results obtained through the VOI method. Group effects in 123I-FP-CIT binding between GD patients and HC were assessed by means of the two sample t-test. The resultant SPM[t] maps were height thresholded at a probability of $p < 0.001$ and an extent threshold of 120 voxels.

2.4 Statistical analysis

Statistical analysis was conducted using SPSS for Windows, Versions 15.0 (SPSS Inc, Chicago, Illinois). All tests were 2-tailed, with statistical significance set at $p < 0.05$. Continuous and categorical variables were expressed as the mean ± standard deviation (SD) and the percentage of the total, respectively. All analyses were conducted using non-parametric testing. Differences between GD patients and HC were assessed with the Chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. The Mann-Whitney U test was employed to compare SPECT and clinical data in GD patients and HC. Spearman's rank correlation coefficient was employed to examine any possible association between continuous variables (i.e., gambling symptoms, psychometric variables and SPECT data). SHAPS and VAS scores were dichotomized using 3 and 5 as cut-off values, respectively.

The Mann-Whitney U test and Spearman's rank correlation coefficient was employed to examine the relationship of IGT scores with dichotomous and continuous variables, respectively.

For these analyses, we did not correct for multiple comparisons, a p-value of less than 0.05 was considered statistically significant. Although multiple tests results were examined, each parameter

was of interest in its own, so we chose to report all individual p-values and make separate statements in relation to our hypotheses. When multiple test results have implications on specific responses, correction for multiple comparisons is not needed, as it is more relevant to know the strength of evidence for testing individual hypotheses (Cook and Farewell, 1996).

3. Results

3.1 Sociodemographic data and psychometric assessment

Sociodemographic and clinical data for GD and HC subjects are presented in **Table 1**.

During the TLFB interview, GD subjects reported 9.13±9.71 days of gambling in the previous month and 14.33±16.81 days from the last gambling episode. GD subjects scored 19.13±9.86 and 23.20±14.33 on the PG-YBOCS and G-SAS, respectively. GD subjects had high levels of trait impulsivity: BIS-11 total score 73.67±7.51 (attentional: 17.93±2.09; motor: 24.33±3.74; non-planning: 31.40±4.26).

GD subjects reported significantly higher hedonic tone dysfunction, as measured with the VAS and SANS. A trend toward significance in SHAPS scores was also observed (**Table 1**), though the two groups did not differ significantly with respect to anhedonia (SHAPS≥3: 6/15 (40%) in the GD group, versus 3/17 (18%) in the HC group). **S1** shows the correlations between the TLFB for gambling, scores on scales for gambling symptoms, hedonic tone, trait impulsivity and mood in GD subjects .

3.2 Striatal DAT availability in GD versus HC

^{123}I-FP-CIT SPECT demonstrated reduced radiotracer uptake in the bilateral striatum of GD subjects, indicative of lower DAT availability (**Figures 1 and 2**). GD subjects had significantly lower DAT binding compared to HC: -13.30% in the right caudate (p=0.011), -11.11% in the right putamen (p=0.021), -11.44% in the left caudate (p=0.036) and -11.46% in the left putamen (p=0.005; **S2**, **Figure 2**).

Moreover a voxel-based whole-brain analysis, performed using SPM, confirmed the VOI analysis results showing reduced 123I-FP-CIT uptake in GD subjects compared with controls in the bilateral striatum (voxel size: 120; peak voxel at 30, -2, 5; p<0.001) (**Figure 3**).

3.3 Correlation of DAT availability with GD symptoms and psychometric assessment

Right putamen and left caudate DAT availability was inversely correlated with number of days spent gambling in the last month (right putamen: R=-0.62; *p*=0.015; left caudate: R=-0.52; *p*=0.049; **Figure 4**). We found a trend towards significance between DAT availability in the right caudate and left putamen and days spent gambling. No correlation was found between striatal DAT availability and other psychometric variables (**S3**).

3.4 Iowa Gambling Task performance: dopaminergic and clinical correlates

Fourteen subjects completed the IGT, with a mean total score of -0.14±23.12 and a final gain of $1607.14±695.83. Selection from decks was as follows: Deck A 18.71±6.34; Deck B 31.36±7.39; Deck C 27.57±7.12; Deck D 22.36±6.78. Scores over the 5 blocks (NET1 to NET5) were as follows: NET1 -0.29±7.6; NET2 -0.29±3.9; NET3 -1.00±6.2; NET4 -0.29±7.8; NET5 1.71±7.3 (**Figure 5**). NET 3-5 scores, most reflective of decision-making strategies, were 0.43±15.25.

Table 2 shows correlation analysis of IGT performance with dopaminergic function (SPECT data) and clinical variables. NET 3-5 scores were positively correlated with bilateral caudate and left putamen DAT binding, while we observed an inverse correlation with number of days spent gambling and G-SAS scores (**Figure 6**).

In addition, we found an inverse correlation between anhedonic symptom severity and IGT total score (**Figure 6**), with a preference for selection from deck B and avoidance of deck C in anhedonic subjects (**Figure 5**).

4. Discussion

4.1 Reduced striatal DAT availability in GD subjects

To our knowledge, this is the first study investigating striatal DAT availability in GD subjects using ^{123}I-FP-CIT SPECT. DAT modulates dopamine temporal dynamics in the synaptic cleft (Vaughan and Foster, 2013). DAT dysregulation thus leads to altered dopamine homeostasis, while at the same time DAT function is crucially dependent on tonic extracellular dopamine concentration. The main finding of our study is reduced striatal DAT availability in GD subjects compared to HC. Our finding significantly expands current knowledge on GD neurobiological underpinnings and confirms the critical involvement of dopaminergic dysfunction in GD pathophysiology, although we cannot draw unambiguous conclusions and must take into account several limitations. Functional neuroimaging studies found reduced ventral striatum DAT concentration in PD patients with GD, though this finding is non-specific as it could denote striatal nerve terminal loss related to PD pathophysiology (Cilia et al., 2010; Voon et al., 2014). Interestingly, our findings are consistent with GD animal models involving dopamine. DAT knockdown mice have been found to exhibit high-reward risk-preference (Young et al., 2011). Furthermore, a gambling-like profile has been experimentally induced by manipulation of DAT expression in rats (Adriani et al., 2010), and DAT down-regulation has been documented in gambling-prone rats (Zoratto et al., 2017). Dopamine dynamics include fast (phasic) firing to salient stimuli and slow changes in tonic concentrations (Dreyer et al., 2010). Striatal dopamine signaling also implies a variation of the phasic rise and fall depending on the expectation of reward/punishment (Schultz et al., 2017). This is accomplished through the mutual effect of different homeostatic mechanisms, including DAT. Our finding can be thus interpreted in the context of tonic/phasic model of dopamine release (Grace, 2000). Gambling behaviors involve prolonged phasic dopamine release (Linnet et al., 2010). To date, studies focusing on targets of dopamine functioning have led to different results in GD compared to SUDs . Our results are consistent with findings in psychostimulant addicts (Ashok et al., 2017). Similarly to cocaine intoxication, reduced DAT function may induce hyperdopaminergic

states after dopamine release. Phasic dopamine release induced by gambling cues and reward anticipation could determine hyperdopaminergic states responsible for high states, excitement, dissociative symptoms and cognitive distortions. In addition, low DAT levels may represent a neurobiological correlate of the reduced dopaminergic tone during gambling withdrawal, consistent with the hyporeactivity reported in resting state fMRI studies (Luijten et al., 2017).

In GD, dopamine-induced DAT down-regulation (Gorentla and Vaughan, 2005) could also underpin the surfacing of negative affective states, which have been hypothesized to trigger compulsivity (Koob and Volkow, 2016). The emergence of negative affective states could mediate the transition from impulsive gambling behavior to gambling addiction. In vulnerable individuals, repeated dopamine release during gambling may down-regulate DAT, determining withdrawal-like symptoms and perpetuating the addiction cycle. Phasic dopamine release induced by reward anticipation possibly compensates for low tonic dopamine states in these subjects (Pettorruso et al., 2014a).

Though studies on dopamine synthesis in GD have yielded mixed results (Boileau et al., 2014; van Holst et al., 2017; Majuri et al., 2017), some evidence points to an increase in dopamine synthesis capacity (van Holst et al., 2017). Also, consistent data points to a similar D2-D3 receptor profile in most GD subjects compared to HC (Boileau et al., 2013; Clark et al., 2012). Taken together, these findings suggest that mostly presynaptic alterations, shaping cortical incentive sensitization processes for monetary rewards (Romer Thomsen et al., 2014), are connected to GD pathophysiology. Changes in presynaptic dopamine release could thus represent neuroadaptations linked to gambling behavioral patterns.

The finding that DAT levels in the right putamen and left caudate were inversely correlated with number of days spent gambling in the last month further supports our hypothesis. Though it does not allow us to draw firm cause-effect conclusions, it is consistent with our contention that recurrent gambling may result in adaptive changes in the dopaminergic system. Possibly, high-frequency gamblers exhibit more severe dopaminergic disruption (i.e., lower DAT). Alternatively, repeated

gambling episodes may determine functional striatal DAT down-regulation by means of epigenetic processes or substrate-mediated post-translational modifications (Zoratto et al., 2017). DAT gene (*SLC6A3*) polymorphisms could impact on striatal activity during reward processing in decision-making and has been associated with different levels of DAT activity in PET e SPECT neuroimaging studies (Faraone et al., 2014). Future studies should consider genetic variability in striatal dopamine neurotransmission, in order to clarify whether reduced DAT availability in GD is linked to a genetic vulnerability factor for addiction, or rather a consequence of a substrate-mediated down-regulation process.

4.2 The potential role of DAT in reward-based decision-making

Our second key finding relates to the possible impact of dopaminergic dysfunction on reward-based decision-making. We found that lower striatal DAT binding was significantly associated with poor performance on the IGT in GD subjects. This allows us to place altered dopamine homeostasis within a decision-making framework, in which relatively high striatal extracellular dopamine levels during anticipation of monetary reward possibly contribute to disadvantageous decision-making (Linnet, 2013).

Executive function and other PFC activities are known to involve dopamine (Nieoullon, 2002). Dopamine contributes to synaptic plasticity in the striatum and the PFC (Chen et al., 2010). Significantly, besides DAT function, synaptic plasticity is also critically dependent on tonic extracellular dopamine concentration (Schultz, 2007). High performance on the IGT possibly reflects more preserved dopamine homeostasis. Alterations causing excessive or low DAT expression could, thus, favor disadvantageous decision-making (van Enkhuizen et al., 2014). During the IGT, GD subjects typically chase larger, immediately rewarding gains, which ultimately lead to long-term losses (Brevers et al., 2013). Moreover, greater striatal dopamine release has been found to predict worse IGT performance in GD subjects (Linnet et al., 2011). It has been suggested

that dopamine codes uncertainty and expected value of reward, rather than reward itself (Linnet et al., 2012). Striatal dopamine release magnitude positively correlates with severity of gambling symptoms in GD (Joutsa et al., 2012). During the IGT, dopamine release has been correlated with excitement levels in GD subjects, but not in controls (Linnet et al., 2011; Linnet et al., 2010). Despite worse IGT performance, GD subjects experience higher excitement. We suggest that dopamine reuptake is involved in the occurrence of maladaptive reward-based decision-making. In light of recent observations of higher dopamine synthesis capacity in GD (van Holst et al., 2017), we hypothesize that increased dopamine release, driven by uncertainty and reward anticipation, is further amplified by reduced DAT clearance and consequent persistence of dopamine in the synaptic cleft, and this coincides with increased excitement and risk propensity.

Finally, we found that GD subjects with anhedonic symptoms performed worse on the IGT. Anhedonia, namely the inability to experience pleasure, could be conceptualized as the inability to respond to positive reinforcement, resulting in significant deficits in reward learning abilities and dysfunctional decision-making. Anhedonic subjects show difficulties in modulating behavior as a function of reward . Studies using fMRI during reward anticipation have shown that GD subjects exhibit differential striatal response to monetary versus natural rewards (Fauth-Buhler et al., 2014; Sescousse et al., 2013). Also, it has been hypothesized that anhedonia is related to gambling severity (Romer Thomsen et al., 2009). Anhedonia could be an important element in the clinical picture of GD, contributing to both poor decision-making and relapse, and its role deserves further studies.

4.3 Limitations

Firstly, small sample size did not allow us to simultaneously control the impact of multiple variables. In addition, it may have hindered detection of relevant correlations between variables explored in the study.

Also, the absence of genetic data (i.e., DAT genetic polymorphisms) and SUDs family history does not allow us to draw conclusions about causal factors involved in low DAT levels in GD subjects. Future studies should further clarify these crucial issues.

Lastly, since SPECT imaging has limited spatial resolution that does not allow to clearly discriminate striatal subregions (i.e., ventral and dorsal striatum), the role of separate striatal subregions in different aspects of reward processing was neglected.

5. Conclusions

Our finding of reduced DAT availability in GD confirms the central role of dopamine dysregulation in this disorder. Gambling "high" may be underpinned by higher dopamine release, as well as longer persistence of dopamine in the synaptic cleft, due to reduced DAT uptake. Our finding may contribute to advancing knowledge on the complex role of dopaminergic dysfunction in GD and provide a possible explanation for inconsistencies reported so far. Possibly, GD is characterized both by hyperdopaminergic and hypodopaminergic states, as part of a sensitized dopaminergic system. The key role of DAT in modulating dopaminergic function, along with other findings from recent studies (Boileau et al., 2014; van Holst et al., 2017), suggest that striatal dopaminergic alterations in GD mainly affect presynaptic functions. Future studies are needed to clarify whether DAT reduction is a predisposing factor for or a consequence of GD.

GD can be conceptualized as a complex addictive disorder underlay by altered frontostriatal connectivity, that influences prefrontal top-down control modulation of reward-related brain areas (Heatherton and Wagner, 2011). A balanced dopaminergic transmission could be crucial in sustaining advantageous decision-making. If the role of DAT down-regulation in GD pathophysiology were to be further confirmed in future studies, this would advocate for treatments that seek to restore striatal dopaminergic transmission (Moccia et al., 2017).

Author contribution

MP, LJ and DDG were primarily responsible for study design. MP, GMar and LDR contributed to data interpretation and article writing. DDG, FC and AC collected and analyzed SPECT data. MP, LM and EC screened and assessed GD patients. MP and GMig performed statistical analysis. MDN and GC were involved in data interpretation. All authors personally revised and approved the final version of the manuscript.

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Table 1. Sociodemographic and clinical data in gambling disorder (GD) patients and healthy controls (HC).

	GD patients	HC subjects	Statistical Analysis	Sig.
N	15	17		
Gender (Male; %)	14 (93.33)	14 (82.35)	3.89[a]	0.143
Age	46.73 ± 13.47	46.18 ± 14.28	126[b]	0.970
Education (*years*)	10.27 ± 2.81	11.76 ± 3.78	97[b]	0.261
Etnicity (Caucasian; %)	15 (100)	17 (100)	NA	NA
Age of Onset	31.87 ± 11.1	-		
Disease Duration	14.87 ± 9.44	-		
Clinical Data				
TLFB Days of Gambling (last month)	9.13 ± 9.71	-		
TLFB Days elapsing from last gambling	14.33 ± 16.81	-		
PG-YBOCS total score	19.13 ± 9.86	-		
Obsession subscale	10 ± 4.53	-		
Compulsion subscale	9.13 ± 5.59	-		
G-SAS	23.20 ± 14.33	-		
Hedonic Tone				
SHAPS Scores	3.2 ± 3.21	1.35 ± 1.50	-1.987	0.053
SHAPS ≥ 3 (n; %)	6 (40)	3 (18)	1.970	0.160
VAS scores	5.1 ± 2.65	2.86 ± 2.79	-2.953	0.003
VAS ≥ 5 (n; %)	6 (40)	2 (12)	3.388	0.066
SANS Anhedonia	9.47 ± 5.2	4.24 ± 7.04	-2.476	0.013
Mood Assessment				
HDRS	6.27 ± 3.95	4.29 ± 2.47	-1.484	0.142
HARS	9.07 ± 4.71	7.18 ± 3.17	-0.949	0.343
YMRS	2.21 ± 1.31	1.59 ± 1.50	-1.362	0.186
BIS-11 total score	73.67 ± 7.51	-		
Attentional	17.93 ± 2.09	-		
Motor	24.33 ± 3.74	-		
Non-Planning	31.40 ± 4.26	-		

Table 2. Iowa Gambling Task (IGT) performance: dopaminergic function and clinical correlates.

	NET1 (1-20)	NET2 (21-40)	NET3 (41-60)	NET4 (61-80)	NET5 (81-100)	TOTAL	GAIN	DECK A	DECK B	DECK C	DECK D	NET 3-5 (41-100)
Dopaminergic function												
Right Caudate	0.436	0.091	0.335	**0.702****	0.254	0.511	0.332	**-0.711****	-0.216	0.306	**0.600***	**0.641***
Right Putamen	0.507	-0.037	0.347	0.508	0.135	0.395	0.326	-0.454	-0.248	0.250	0.463	0.507
Left Caudate	**0.540***	0.174	0.379	**0.773****	0.233	**0.596***	0.402	**-0.746****	-0.324	0.395	**0.643***	**0.659***
Left Putamen	**0.560***	0.163	0.351	**0.613***	0.343	**0.584***	0.392	**-0.725****	-0.283	0.444	0.531	**0.634***
Gambling symptoms												
Days of gambling	-0.350	-0.099	**-0.676****	-0.317	-0.231	-0.433	**-0.588***	0.344	0.350	-0.296	-0.430	**-0.592***
G-SAS	-0.170	-0.169	**-0.552***	-0.169	-0.223	-0.396	-0.029	0.170	0.397	-0.162	-0.464	**-0.596***
Hedonic Tone												
SHAPS	**-0.689****	**-0.625***	-0.374	-0.316	-0.297	**-0.680****	-0.154	**0.583***	**0.549***	**-0.805****	-0.229	-0.486
SHAPS ≥ 3[a]	9.50	**4.00***	11.00	18.50	9.00	**5.50***	19.00	11.50	**5.50***	**2.50****	17.00	10.00
VAS ≥ 5 [a]	14.50	13.50	11.00	15.50	14.50	11.00	13.00	16.50	**8.50***	11.50	12.50	9.50

[a] Mann-Whitney U Test. *p<0.05. **p<0.01.