

University of Groningen

No evidence for decreased D2/3 receptor availability and frontal hypoperfusion in subjects with compulsive pornography use

Stormezand, Gilles N; Doorduyn, Janine; Chaves, Lumi T; Vallez Garca, David; Nienhuis, Fokko J; Schoevers, Robert A; Kremer, Berry P H; Booij, Jan; Dierckx, Rudi A J O

Published in:
Psychiatry research-Neuroimaging

DOI:
[10.1016/j.psychresns.2021.111284](https://doi.org/10.1016/j.psychresns.2021.111284)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Stormezand, G. N., Doorduyn, J., Chaves, L. T., Vallez Garca, D., Nienhuis, F. J., Schoevers, R. A., Kremer, B. P. H., Booij, J., & Dierckx, R. A. J. O. (2021). No evidence for decreased D2/3 receptor availability and frontal hypoperfusion in subjects with compulsive pornography use. *Psychiatry research-Neuroimaging*, 311, [111284]. <https://doi.org/10.1016/j.psychresns.2021.111284>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

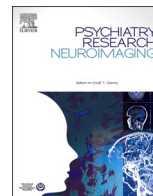
Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

No evidence for decreased D2/3 receptor availability and frontal hypoperfusion in subjects with compulsive pornography use

Gilles N. Stormezand^{a,*}, Janine Doorduyn^a, Lumi T. Chaves^a, David Vázquez García^a,
Fokko J. Nienhuis^b, Robert A. Schoevers^b, Berry P.H. Kremer^c, Jan Booij^d, Rudi A.J.
O. Dierckx^a

^a Department of Nuclear Medicine and Molecular Imaging, Medical Imaging Center, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

^b Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

^c Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

^d Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location Academic Medical Center, Amsterdam, Netherlands

ARTICLE INFO

Keywords:

Dopaminergic imaging
Pornographic addiction
Cerebral blood flow

ABSTRACT

Pornographic addiction refers to an addiction model associated with compulsive and repeated use of pornographic material. Whether the use of pornography may indeed become addictive remains a matter of debate. The current study investigated whether compulsive pornography use (CPU) is accompanied by reduced D2/3 receptor availability in the striatum and frontal hypofunctionality. Male subjects between 18 and 50 years of age with and without CPU were recruited using online and newspaper advertisements. Questionnaires were used to assess the severity of compulsive pornography use (CIUS) and symptoms of depression, impulsivity and sensation seeking. Dopaminergic imaging was performed using [11C]-raclopride PET. Striatal binding potentials (BPND) and regional frontal cerebral influx values (R1) of [11C]-raclopride were calculated. Arterial Spin Labeling (ASL) MRI was performed to assess regional cerebral blood flow. No group differences between striatal BPND's of [11C]-raclopride in subjects with ($n = 15$) and without ($n = 10$) CPU were detected. In CPU subjects, no correlation was found between the CIUS score and striatal BPND's. Cerebral R1 values in frontal brain regions and cerebral blood flow measurements did not differ between groups. The current study fails to provide imaging support for sharing similar neurobiological alterations as previously has been reported in other addictive modalities.

1. Introduction

Pornographic addiction (PA) refers to a (behavioral) addiction model associated with compulsive and repeated use of pornographic material (de Alarcon et al., 2019). Similar to other individuals suffering from addiction, patients with PA may show symptoms of craving and diminished self-control (Kor et al., 2013). Online surveys indicate that between 5 and 9% of participants may experience problematic use of internet pornography, leading to functional impairments in social, psychological and occupational domains. These problems tend to be more prevalent in men (Cooper et al., 2004; Ross et al., 2012). In the past, pornographic material used included videos, DVDs and magazines, but with the expansion of the internet these are on the decline. Indeed,

internet pornography is rapidly expanding (Bancroft, 2008). Certain characteristics of the internet such as accessibility, affordability and anonymity, referred to as a 'triple A engine' (Cooper, 1998), may greatly facilitate the development of compulsive use of online erotica.

Whether the use of (internet) pornography may indeed become addictive remains a matter of debate. In the literature, a broad spectrum of terminology has been used to describe excessive sexual behavior, including perversions, paraphilias, compulsive sexual behaviors (Coleman et al., 2003), impulse control disorders (ICD) (Barth and Kinder, 1987), and sexual addictions (Orford, 1978). Diagnostic criteria for DSM-5 have been considered for 'hypersexuality disorder', adopting many of the dimensions which are typically utilized in diagnosing addictive disorders (Kafka, 2010). In a DSM-5 field trial for

* Corresponding author: G.N. Stormezand, Department of Nuclear Medicine and Molecular Imaging University of Groningen University Medical Center Groningen Hanzeplein 1 9700 RB, Groningen, the Netherlands.

E-mail address: g.n.stormezand01@umcg.nl (G.N. Stormezand).

<https://doi.org/10.1016/j.psychresns.2021.111284>

Received 19 August 2020; Received in revised form 19 March 2021; Accepted 19 March 2021

Available online 22 March 2021

0925-4927/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

hypersexuality disorder, pornography consumption was the most predominant behavior (81.1%) (Reid et al., 2012). Analogous to many drug addictions, hypersexuality may escalate in the course of the disorder, withdrawal symptoms may be present, and it may be difficult to reduce the frequency of sexual behavior. In addition, it has been suggested that a craving state may be present prior to initiation of the behavior and that loss of control may preclude the subject from discontinuing the behavior despite adverse consequences (Potenza, 2006). Comorbidities with psychiatric disorders are frequently observed, most commonly mood disorders (72%), anxiety disorders (38%) and substance use disorder (SUD) (40%) (Kafka and Hennen, 2002).

Despite the presence of these similarities with drug addiction, it is difficult to define a pathologic addictive state related to the use of internet pornography, since sexual behavior, including viewing of online erotica, may be considered normal behavior. To illustrate this, it has been estimated that 98% of males and 74–80% of females have viewed pornography at least once in their lives (Hald and Malamuth, 2008; Svedin et al., 2011). Currently, gambling disorder remains the only behavioral addiction included in the DSM-5 section 'substance disorders and other addictive behaviors' (American Psychiatric Association, 2013), as it has been shown that there are similarities between pathological gambling disorder and SUDs (Petry, 2006; Potenza, 2006). A need for studies aiming to identify neurobiological substrates of hypersexuality disorders has been expressed in order to allow comparison to SUD (Kor et al., 2013).

Altered dopamine transmission has been assumed to play a critical role in the pathogenesis of addiction (Koob and Volkow, 2010). In particular, dopamine D₂ receptors are associated with addiction-linked processes such as reward seeking, prediction, expectation, and motivation (Wise, 2006). Dopamine D₂ receptors are predominantly present in the striatum, in the core of the nucleus accumbens (NAc), and in the olfactory tubercle, but they are also expressed in the prefrontal, cingulate, temporal and entorhinal cortices, amygdala, hippocampus, hypothalamus, substantia nigra pars compacta and the ventral tegmental area (Missale et al., 1998).

Positron emission tomography (PET), using [¹¹C]-raclopride as a radioligand, enables functional assessment of dopamine D_{2/3} receptor availability. Decreased [¹¹C]-raclopride binding has been a consistent finding in studies assessing the dopamine D_{2/3} receptor availability in the striatum in subjects addicted to substances including cocaine (Martinez et al., 2004a; Volkow et al., 1997), methamphetamine (Lee et al., 2009; Volkow et al., 2001), alcohol (Hietala et al., 1994; Volkow et al., 1996) and heroin (Martinez et al., 2012). In these cases, the lower level of D_{2/3}-receptor availability on a group level in addicts may reflect a vulnerability for addiction as well as a decreased sensitivity for naturally occurring rewards, a condition which has been described as the 'reward deficiency syndrome' (Blum et al., 2000). Likewise, the behavioral addiction gambling disorder has been linked to a decreased sensitivity to natural reinforcers. In spite of this commonality between SUD and GD, several studies failed to detect reduced D_{2/3} receptor availability at baseline in GD (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Linnet et al., 2010). Currently, the D_{2/3} receptor availability in pornographic addiction has not yet been investigated.

In metamphetamine abusers, a reduction of baseline D_{2/3} receptor availability was associated with decreased glucose metabolism in the orbitofrontal cortex (Volkow et al., 2001), which could reflect a deficit in prefrontal inhibitory signaling towards the striatum (Chambers et al., 2009). Dysfunction of the prefrontal cortex has been associated with a wide range of disadvantageous behaviors in addiction (Goldstein and Volkow, 2011), including impulsivity, compulsivity and impaired self-monitoring, which may also play a role in pornographic addiction.

The current study hypothesizes that CPU is accompanied by reduced dopamine D_{2/3} receptor availability in the striatum and frontal hypo-functionality. If this is the case, it would provide support for the concept that PA shares neurobiological alterations similar to those observed in SUD's.

2. Methods

2.1. Participants

Male participants between 18 and 50 years of age were recruited using online (social media) and newspaper advertisements, calling for volunteers who identified as having 'pornographic addiction' or 'problematic use of internet pornography' and a control group without problematic use of internet pornography. All subjects were asked to fill out questionnaires related to compulsive internet pornography use, depressive symptoms, impulsivity and sensation seeking. In addition, a general questionnaire was developed by the investigators, involving questions about sociodemographic characteristics, medication, use of alcohol and cigarettes, medication and psychiatric disease history. Exclusion criteria included lifetime DSM-IV axis I disorder, drug dependence or abuse, including alcohol (i.e. drinking more than 30 drinks per month or any illicit drug use during the past 30 days), active medical condition, treatment in the last 6 months with antidepressants, neuroleptics, sedative hypnotics, glucocorticoids, appetite suppressants, sex hormone, opiate or dopaminergic medication, use of psychoactive medications within the past 30 days, lifetime history of seizure disorder or closed head trauma, participation in a scientific research study (<1 year) involving radiation and contra-indications for MRI-scanning. During the screening procedure those subjects that best fitted the profile of 'isolated' CPU were selected from the respondents ($n = 250$). To be included in the study subjects were required to report a high score (40 or higher) on the modified compulsive internet use scale (CIUS; for details see below) and no significant comorbidities or use of addictive substances. Subjects included for CPU ($n = 16$) underwent additional screening by a clinical psychologist (F.N.) to rule out (history of) co-existing addictions (e.g. SUD) and lifetime axis-I disorders using a structured interviewing approach (MINI) (Sheehan et al., 1998), with the exception of depressive disorder ($n = 6$). A total of 15 heterosexual male subjects with CPU and 10 without CPU were eventually included in the study. Written informed consent was given by each individual and the study was approved by the local ethics committee at the UMCG (NL48500.042.14).

2.2. Questionnaires

2.2.1. Compulsive internet pornography use

The modified CIUS was used to assess the presence and severity of compulsive use of internet pornography. The CIUS was developed by Meerkerk and co-workers to determine compulsive internet use, and found to be a reliable and valid instrument with high internal consistency (Downing et al., 2014; Meerkerk et al., 2009). The scale consists of 14 questions (in Dutch) and answers to these questions can be given on a 5-point Likert Scale. The items do not measure the time involved in the consumption of pornography directly, but are focused on related compulsive, uncontrolled, excessive and obsessive aspects of the behavior. Higher scores have been positively correlated with relevant variables including sexual sensation seeking, boredom, sexual frustration and time spent viewing internet pornography (Downing Jr et al., 2014). A previous survey conducted by the IVO addiction research institute reported that an average score of 3 or higher each of these questions (or a total score of 42) was present in only 0.7% of the population ($n = 1839$) and therefore may be considered 'high'. A similar score on a modified version of the CIUS was shown to be indicative of compulsivity in online gaming (van Rooij et al., 2011). Although no formally validated cut-off score is available to define CPU, a comparably high score was thus used in this study for the inclusion of subjects with CPU. The minimum score on the CIUS is 14 (score of 1 on every question).

2.2.2. Depression

The self-report version of the 30-item Inventory of Depressive

Symptomatology (IDS-SR30) was used to assess the severity of depressive symptoms. It has been reported to have a high internal consistency and highly acceptable psychometric properties (Trivedi et al., 2004).

2.2.3. Impulsivity

The revised Barrett-Impulsivity-Scale (BIS)-11 scale was used to score impulsivity in each individual, which has been shown to provide internally consistent measurements of impulsiveness (Patton et al., 1995).

2.2.4. Sensation seeking

Zuckerman's Sensation Seeking Scale-V (Zuckerman et al., 1978) was used to assess the trait of sensation seeking. It has high internal consistency and its convergent validity has been supported (Roberti et al., 2003).

2.3. Imaging

Dopaminergic imaging was performed using the well-validated PET tracer [¹¹C]-raclopride, which is a selective dopamine D_{2/3} receptor antagonist. Subjects were asked to refrain from smoking and drinking of alcohol for 24 h and not to eat in the 4 h prior to the PET scan. Striatal dopamine D_{2/3} receptor availability was measured following a 60 min dynamic acquisition protocol after a 1 min bolus injection of approximately 200 (197 ± 15) MBq of [¹¹C]-raclopride on a Siemens Biograph mCT system (Siemens Medical Solutions USA, Inc) with the head immobilized in a headrest to reduce motion artifacts. [¹¹C]-raclopride was prepared using [¹¹C]-methyl iodide according to a previously described protocol (Ehrin et al., 1987). Molar activity of [¹¹C]-raclopride was always more than 20,000 GBq/mmol and radiochemical purity was higher than 95%. Images were dynamically acquired with the following time frames (frame 1–7: 10 s, frame 8–9: 30 s, frame 10–12: 60 s, frame 13–14: 120 s, frame 15–16: 180 s, frame 17–18: 180 s, frame 19–23: 300 s, frame 24–25: 600 s) with the injection 10 s prior to the scanning procedure. Images were reconstructed using Truex+TOF with 3 iterations and 21 subsets in a 400 × 400 matrix size (zoom 1.0). All PET images were coregistered to an individual anatomical 1 mm isotropic 3D T1 MRI performed on a 3 Tesla Siemens Prisma MRI system (Siemens Medical Solutions USA, Inc), with the head immobilized, and spatially normalized to Montreal Neurological Institute (MNI) space using PMOD (version 4.0, PMOD Technologies Ltd, Zürich, Switzerland). Brain regions were defined using the Hammers maximum probability atlas (Hammers N3083). Time activity curves (TAC's) were computed for the caudate nucleus, nucleus accumbens, putamen, dorsal striatum (caudate nucleus and putamen combined), the whole striatum and the cerebellum. For each patient, the binding potential (BP_{ND}) was calculated, and used as outcome measure, using a simplified reference tissue model with the cerebellum as the reference region (Innis et al., 2007). Using the same model, the local cerebral influx ratio R1 (K1/K'1) was calculated for the frontal lobes, in particular the middle frontal gyrus and orbito-frontal cortices. Group level comparisons were performed using independent sample t-tests, correcting for multiple comparisons (Bonferroni correction for each investigated brain region, $p < 0.05$ considered significant). For statistical analysis, SPSS was used (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Correlations between regional BP_{ND} and the scores on the questionnaires were assessed using scatter plots and linear regression analysis using GraphPad Prism version 7.02 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

Pseudo-continuous arterial Spin Labeling (ASL) MRI (Detre et al., 2009) was performed to assess regional cerebral blood flow – as a surrogate marker of functionality - using the standard sequence provided by the vendor. Resting state whole brain perfusion images were acquired using high-resolution ASL 3D GRASE. During each acquisition, 4 pairs of label-control images were obtained while the subjects were resting with their eyes closed. All perfusion images were coregistered to the

anatomical 3D T1 MRI (MPRAGE), realigned and spatially normalized. Group-wise voxel-based comparison was carried out using SPM 12 (2-sample T-test, no mask, $p < 0.001$ (no minimum number of voxels) or $p < 0.05$ with FWE correction) considered significant).

3. Results

Patient characteristics are shown in Table 1. The mean ages were 32.2 ± 2.2 for the group with CPU and 30.6 ± 3.3 years for the control group ($p = 0.67$). Subjects with problematic use of internet pornography showed significantly higher scores on the modified CIUS (49.4 in the PA group vs. 17.5 in the control group), questionnaires assessing impulsivity and depression (p values < 0.01), including factors mood/cognition, anxiety/arousal and sleep. Details of the scores on the modified CIUS in both groups are provided in Table 4, supplemental data.

Fig. 1 shows a representative example of the acquired PET and MRI images as well as the time activity curves (TACS) of a receptor-rich region (striatum) and the reference region (cerebellum). No group differences between the mean binding potential (BP_{ND}) of [¹¹C]-raclopride in subjects with and without problematic pornography were detected in any region (Table 2). In subjects with problematic internet pornography use, no correlation was found between the CIUS score - indicating the severity of the compulsive behavior - and the binding potential of [¹¹C]-raclopride in all investigated regions of the brain (Fig. 2). The binding potential in the striatum was not significantly influenced by scores on depression, sensation seeking or impulsivity (Fig. 3). The cerebral influx values R1 in frontal brain regions did not differ significantly between subjects and controls (supplemental data, Table 3).

No significant clusters with increased or reduced cerebral perfusion ($p < 0.001$ no threshold or $p < 0.05$ FWE corrected) were observed when comparing the normalized ASL perfusion images between groups. Despite our efforts to as much as possible include subjects with isolated CPU, six patients were screened positive for lifetime depressive disorder. One subject admitted to smoke two cigarettes per day. Exclusion of these subjects however did not lead to significant group differences in all investigated parameters.

4. Discussion

In this study no statistically significant differences in striatal dopamine D_{2/3} receptor availability or frontal cerebral influx of [¹¹C]-raclopride were observed in patients with and without problematic use of internet pornography. Also, no regional cerebral perfusion differences in the frontal brain areas between these groups were identified. On a group level, patients with CPU had more depressive symptoms, were more impulsive and tended to have more sensation seeking traits compared to the age-matched control group.

The failure to demonstrate reduced striatal dopamine D_{2/3} receptor availability largely contrasts with previous findings in groups with

Table 1
Patient characteristics.

	CPU subjects	Controls	p value (t-test)
Mean age (years)	32.2 (2.2)	30.6 (3.3)	0.67
Sex (male,%)	100	100	n/a
CIUS score	49.4 (2.2)	17.5 (1.0)	<0.01
BIS-11	66.8 (3.2)	51.4 (2.4)	<0.01
- attentional	18.8 (1.2)	12.7 (1.0)	<0.01
- motor	23.8 (1.1)	20.6 (1.0)	0.05
- nonplanning	24.2 (1.3)	18.1 (0.9)	<0.01
Sensation seeking	211.27 (6.9)	196.3 (8.9)	0.20
Depression score	21.4 (3.0)	3.6 (1.1)	<0.01
- mood/cognition	7.7 (1.5)	0.6(0.2)	<0.01
- anxiety/arousal	5.8(1.0)	0.8(0.3)	<0.01
- sleep	2.9(0.6)	0.9(0.5)	0.03
Smoking (n, cigarettes per day)	1 (2)	0	0.33

Data are displayed in means with the standard error of the mean.

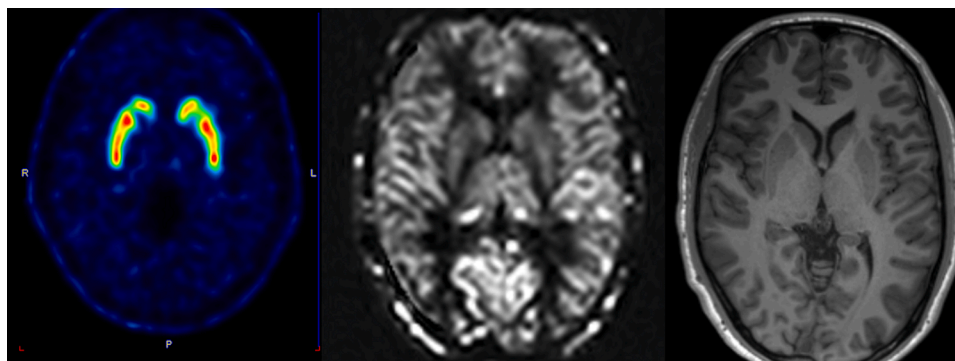


Fig. 1. Representative example of a $[^{11}\text{C}]$ -Raclopride PET (23 frame average), reconstructed ASL MRI perfusion image and T1 anatomical MRI of a subject.

Table 2

Mean binding potential (BP_{ND} and SEM) of $[^{11}\text{C}]$ -raclopride PET in CPU subjects and controls.

Brain region	CPU subjects ($n = 15$)	Controls ($n = 10$)	p value (t -test)
Caudate nucleus	2.28 (0.17)	2.51(0.16)	0.38
- Left	2.24 (0.19)	2.52(0.12)	0.28
- Right	2.33(0.16)	2.49(0.23)	0.57
Nucleus accumbens	2.07(0.09)	1.74(0.11)	0.03*
- Left	2.08(0.14)	1.87(0.10)	0.28
- Right	2.17(0.15)	1.66(0.22)	0.06
Putamen	3.58 (0.11)	3.49(0.14)	0.59
- Left	3.59 (0.10)	3.45(0.15)	0.39
- Right	3.57(0.12)	3.53(0.13)	0.79
Dorsal striatum	2.95(0.14)	3.01(0.14)	0.76
- Left	2.94(0.14)	3.00(0.12)	0.74
- Right	2.96(0.14)	3.02+(-0.17)	0.80
Whole striatum	2.92(0.13)	2.96(0.14)	0.82
- Left	2.90(0.13)	2.96(0.11)	0.77
- Right	2.94(0.13)	2.97(0.17)	0.87

* not significant after correcting for multiple comparisons.

SUDs, in which decreased striatal $[^{11}\text{C}]$ -raclopride binding has been a consistent finding (Hietala et al., 1994; Lee et al., 2009; Martinez et al., 2012, 2004b; Volkow et al., 2001, 1997, 1996). Few studies failed to report dopamine $\text{D}_{2/3}$ receptor related differences in SUD compared to controls, particularly involving studies on alcohol and nicotine abuse (Montgomery et al., 2007; Spreckelmeyer et al., 2011). However, the finding of reduced striatal $\text{D}_{2/3}$ receptor availability has been less consistently reported in ‘behavioral’ addictions, with several reports showing no alterations in $\text{D}_{2/3}$ receptor availability in subjects with gambling disorder in comparison to controls (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Linnert et al., 2010). In binge eating disorder, no changes in baseline $[^{11}\text{C}]$ -raclopride binding were observed in subjects compared to controls, although a higher food-related decline in BP_{nd} was seen in binge eaters than in non binge eaters (Wang et al., 2011). In some other forms of behavioral addictions, $\text{D}_{2/3}$ reductions have been reported, Reduced striatal $\text{D}_{2/3}$ receptor availability has been shown in the dorsal striatum of subjects with compulsive internet use (Kim et al., 2011). From the latter study, it could however not be estimated which specific online activity was related to the observed differences in $\text{D}_{2/3}$ -receptor availability. It should also be noted, that this was a small study that included only 5 male subjects with internet addiction. In 2014, a larger study reported lowered putaminal D_2 receptor levels in a group with internet gaming disorder ($n = 12$) in comparison to healthy controls ($n = 14$), but only in relation to an internet gaming task and not at baseline (Tian et al., 2014a). Thus, it seems that the absence of a significant decrease in $\text{D}_{2/3}$ receptor availability in CPU subjects is largely in accordance with what has been observed in behavioral addictions. Previously, it has been suggested that while sharing a general vulnerability, the supraphysiological dopamine

releases generated by substances may be responsible for a neuroadaptive process that is different from the behavioral addiction gambling disorder (Clark et al., 2019). This could explain the lack of differences in $\text{D}_{2/3}$ receptor availability between CPU subjects and controls in our study, despite showing higher scores on impulsivity and depression.

Although no significant differences in striatal BP_{ND} were found after correcting for multiple comparisons, subjects with CPU in our study tended to show higher binding in the nucleus accumbens ($p = 0.03$, uncorrected). In the ventral striatum, increased binding of $[^{11}\text{C}]$ -raclopride may reflect increased D_3 receptor availability, as this receptor is particularly abundant in this region (Gurevich and Joyce, 1999). A hyperdopaminergic state related to the D_3 receptor has been linked to ICD in Parkinson’s disease (PD), particularly as a consequence of treatment with dopamine receptor agonists with high D_3 affinity (Kelley et al., 2012). In PD subjects with ICD increased cue-induced dopamine release was reported in the ventral striatum (Steeves et al., 2009). Using $[^{11}\text{C}]$ -PHNO PET in subjects with SUD, increased binding was reported in D_3 rich regions associated with impulsivity (Payer et al., 2014), but this was not observed in another study in PD patients with ICD (Payer et al., 2015). In PD however, an upregulation of $[^{11}\text{C}]$ -PHNO may be masked by loss of presynaptic dopaminergic neurons in the substantia nigra. In our investigation, subjects with CPU scored significantly higher on the BIS-11 impulsivity scale. However, no significant correlation was found between impulsivity scores and BP_{ND} in the nucleus accumbens. Second, increased $[^{11}\text{C}]$ -raclopride uptake may also indicate decreased basal dopaminergic firing tone along with increased $\text{D}_{2/3}$ receptor density, both factors which increase $\text{D}_{2/3}$ receptor availability. Therefore, the potential link between D_3 receptor upregulation in the nucleus accumbens and ICD in subjects with CPU should be interpreted with caution.

Another aim of this study was the investigation of ‘hypofrontality’ using $[^{11}\text{C}]$ -raclopride cerebral influx values (R1) and potential regional cerebral blood flow reductions by means of ASL MRI, especially in the prefrontal area, which could reflect the inability to suppress the undesired compulsive behavior. However, we did not find reduced R1 values nor perfusion alterations in these areas in subjects with PA using ASL MRI voxel based comparisons during the resting state. These results contrast with previous findings reported by Tian et al. in internet gaming disorder, who observed decreased metabolism in prefrontal, temporal and limbic regions using $[^{18}\text{F}]$ -FDG PET ($p < 0.01$ uncorrected, minimum cluster size 100 voxels) (Tian et al., 2014b). In the same group, lowered D_2 receptor levels were reported, using the PET ligand (11)C-N-methylspiperone ((11)C-NMSP), which correlated with hypo-metabolism in the orbitofrontal cortex. The combination of findings was suggestive of disturbances in striatal prefrontal pathways and has also been demonstrated in SUD (Volkow et al., 2001). In cocaine abusers, increased amphetamine induced metabolism in these regions was associated with craving (Volkow et al., 2005). Using ASL MRI alone in adolescent subjects with gaming disorder, multiple clusters with significantly increased or decreased CBF were observed during resting

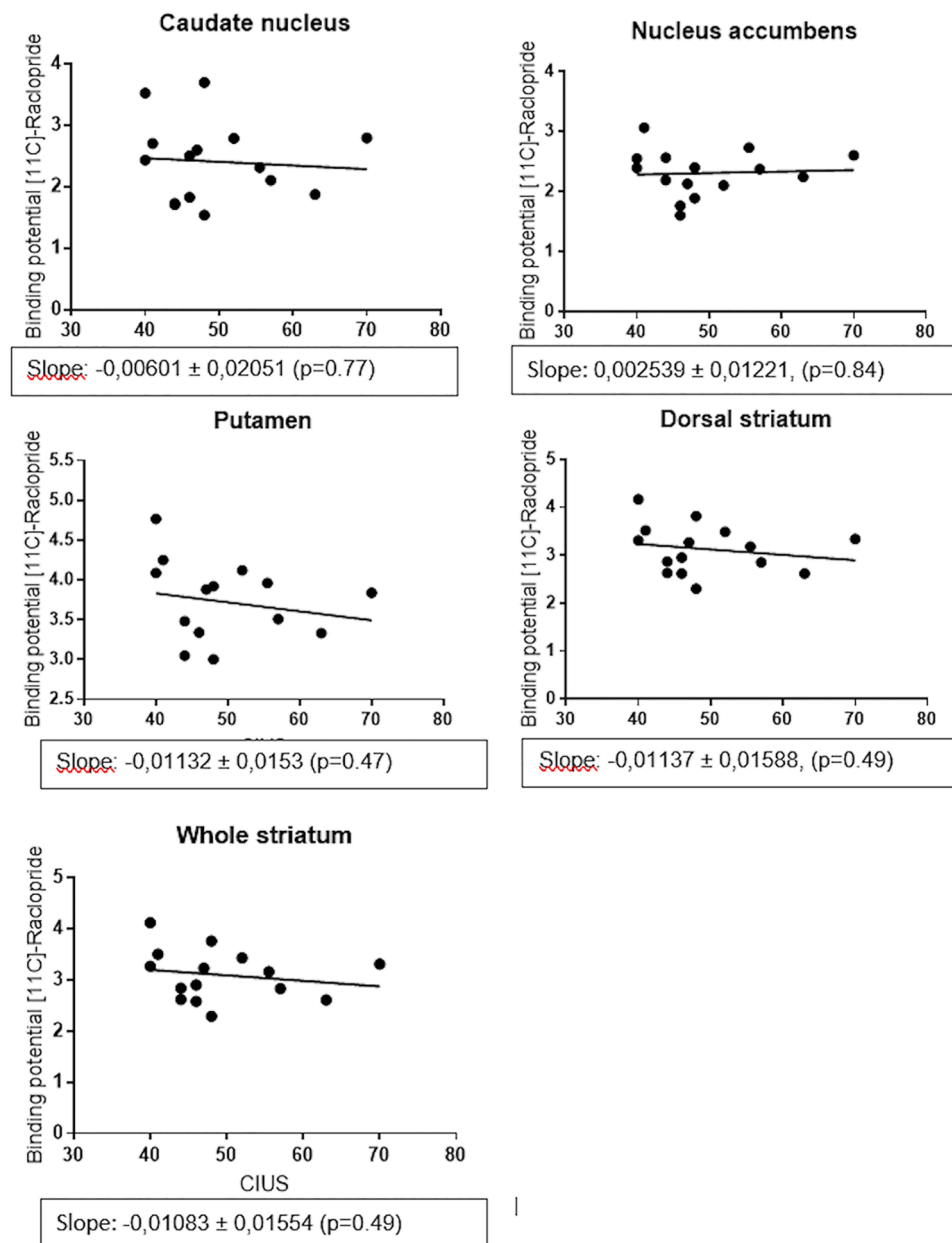


Fig. 2. Scatterplots and regression analysis of $[^{11}\text{C}]$ -raclopride BP_{ND} and scores on the modified CIUS in subjects with CPU.

state in regions assumed to play a role in the addiction model (Feng et al., 2013a). In pathologic gambling however, opposing results have been reported, with increased relative glucose metabolic rates in the orbitofrontal cortex and medial frontal cortex (Hollander et al., 2008). A review evaluating results of another modality (fMRI) in behavioral addictions, concluded that the evidence for hypoactivity of the frontal cortex was scarce and not yet conclusive (Luijten et al., 2014).

5. Limitations

One of the limitations of the current study is the small sample size, which may have obscured small differences in striatal dopamine $\text{D}_{2/3}$ receptor availability between both groups. The sample size is however comparable to previous work in the field (Boileau et al., 2013; Clark et al., 2012) and adequate to facilitate the ‘proof of principle’ approach of this study. Another limitation is that no validated cut-off point for the modified CIUS score to identify a subject as positive for CPU is available. However, previous work showed that the scores on the modified CIUS

obtained by CPU subjects in our sample may be considered ‘high’ (uncommon in the general population) and that similar scores on an adapted version of the CIUS were indicative of compulsivity in online gaming (van Rooij et al., 2011). As the severity of problematic use of internet pornography was not clearly correlated to $\text{D}_{2/3}$ receptor availability in our sample, it is unlikely that a higher – more stringent - cut-off point would have led to different results. Given the fact that currently no validated criteria for the diagnosis of PA or CPU exist, it seems likely that future research will suffer from similar limitations when it comes to the inclusion criteria. In this respect, previous research has pointed out that it also may be difficult to acquire a control group, as the viewing of online erotica may be considered normal behavior. Our control group however did not disclose significant consequences of compulsive nature. Also, both groups consisted of male subjects only, which could limit the generalizability of the findings.

Although previous neuroimaging studies investigating $\text{D}_{2/3}$ receptor and metabolism in SUD’s used a combination of $[^{11}\text{C}]$ -raclopride and $[^{18}\text{F}]$ -FDG, we used ASL MRI and R1 values of $[^{11}\text{C}]$ -raclopride as a

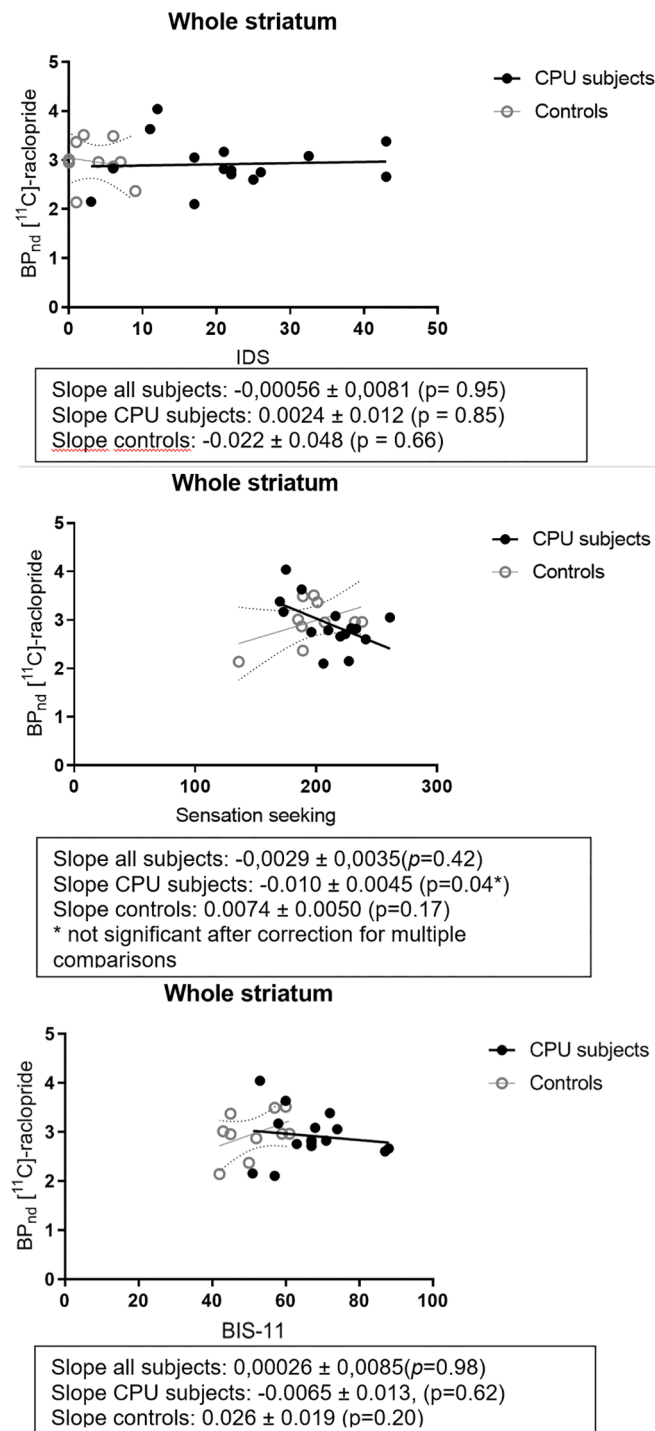


Fig. 3. Scatterplots and regression analysis of [¹¹C]-raclopride BP_{ND} and scores on depression, sensation seeking and impulsivity in the whole striatum.

marker of frontal functioning. ASL MRI has the advantage over [18F]-FDG that it uses magnetically labeled water protons as a form of endogenous contrast and therefore limits the exposure of subjects to ionizing radiation. The feasibility of ASL to detect abnormalities associated with behavioral addictions has previously been demonstrated in adolescent subjects with gaming disorder (Feng et al., 2013b). Although no direct comparative studies are available which have investigated R1 values in subjects with SUD's or behavioral addictions, it has been used as a proxy measure of cerebral blood flow in the field of neurodegenerative diseases (van Laere et al., 2010). Finally, we performed D_{2/3} receptor imaging only in 'resting state'. Despite the fact that the

procedure was performed under standardized circumstances (e.g. refraining from alcohol, smoking and eating), it cannot be ruled out that the release of endogenous dopamine, induced e.g., by the administration of the dopamine releaser amphetamine, is different between both groups. In addition, we did not perform dynamic imaging in response to cues (e.g. visual stimuli of erotic nature), during which altered dopamine release could have become apparent.

Thus, our failure to detect a neurobiological fingerprint of CPU that is similar to what has been established for other forms of addiction, may result from methodological limitations. But, more likely, these findings may reflect different neurobiological mechanisms that contrast this form of addiction with other addictive modalities, mainly SUD.

Conclusion

No significant differences in striatal D_{2/3} receptor availability, frontal cerebral influx of [¹¹C]-raclopride or cerebral prefrontal perfusion between subjects with and without compulsive use of internet pornography could be detected. The current study fails to provide imaging support for sharing similar neurobiological alterations as previously has been reported in SUD.

Contributors

Gilles N. Stormezand: Conceptualization, Formal analysis, Writing-original draft, Visualization. Janine Doorduyn: Conceptualization, Formal analysis, Writing – original draft. Lumi T. Chaves: Conceptualization, Formal analysis, Writing - original draft. Fokko J. Nienhuis: Conceptualization, Methodology. David Vázquez García: Methodology, Visualization, Writing – Original draft.. Robert A. Schoevers – Conceptualization, Writing – Original draft. Berry P.H. Kremer: Supervision, Writing- Original draft. Jan Booij: Methodology, Writing – Original draft. Rudi A.J.O. Dierckx: Conceptualization, Supervision, Writing – original draft

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgement

We thank Gert-Jan Meerkerk of the IVO Addiction Research Institute Rotterdam, The Netherlands Erasmus Medical Center Rotterdam, The Netherlands, for his cooperation and sharing of his knowledge and experience in the field.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.111284](https://doi.org/10.1016/j.psychres.2021.111284).

References

- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental disorders : DSM-5*. American Psychiatric Association, Arlington, VA.
- Bancroft, J., 2008. Sexual behavior that is "out of control": a theoretical conceptual approach. *Psychiatr. Clin. North Am.* 31, 593–601. <https://doi.org/10.1016/j.psc.2008.06.009>, 10.1016/j.psc.2008.06.009.
- Barth, R.J., Kinder, B.N., 1987. The mislabeling of sexual impulsivity. *J Sex Marital Ther* 13, 15–23. <https://doi.org/10.1080/00926238708403875>.
- Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J. O., Chen, T.J., Comings, D.E., 2000. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive

- behaviors. *J Psychoactive Drugs* 32, 1–112. <https://doi.org/10.1080/02791072.2000.10736099>. Suppl, i–iv[doi].
- Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P.M., Houle, S., Wilson, A.A., Warsh, J., Kish, S.J., Zack, M., 2013. The D2/3 dopamine receptor in pathological gambling: a positron emission tomography study with [¹¹C]-(+)-propyl-hexahydro-naphtho-oaxazin and [¹¹C]raclopride. *Addiction* 108, 953–963. <https://doi.org/10.1111/add.12066> [doi].
- Chambers, C.D., Garavan, H., Bellgrove, M.A., 2009. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* 33, 631–646. <https://doi.org/10.1016/j.neubiorev.2008.08.016> [doi].
- Clark, L., Boileau, I., Zack, M., 2019. Neuroimaging of reward mechanisms in Gambling disorder: an integrative review. *Mol. Psychiatry* 24, 674–693. <https://doi.org/10.1038/s41380-018-0230-2> [doi].
- Clark, L., Stokes, P.R., Wu, K., Michalczuk, R., Bence, A., Watson, B.J., Egerton, A., Piccini, P., Nutt, D.J., Bowden-Jones, H., Lingford-Hughes, A.R., 2012. Striatal dopamine D(2)/D(3) receptor binding in pathological gambling is correlated with mood-related impulsivity. *Neuroimage* 63, 40–46. <https://doi.org/10.1016/j.neuroimage.2012.06.067> [doi].
- Coleman, E., Raymond, N., McBean, A., 2003. Assessment and treatment of compulsive sexual behavior. *Minn Med* 86, 42–47.
- Cooper, A., 1998. Surfing into the new millenium. *Cyberpsychol. Behav.* 1, 181–187.
- Cooper, A., Delmonico, D.L., Griffin-Shelley, E., Mathy, R.M., 2004. Online sexual activity: an examination of potentially problematic behaviors. *Sex Addiction Compulsivity: The Journal of Treatment & Prevention* 11, 129–143.
- de Alarcón, R., de la Iglesia, J.I., Casado, N.M., Montejo, A.L., 2019. Online porn addiction: what we know and what we don't—a systematic review. *J Clin Med* 8. <https://doi.org/10.3390/jcm8010091> <https://doi.org/E91> [pii].
- Detre, J.A., Wang, J., Wang, Z., Rao, H., 2009. Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. *Curr. Opin. Neurol.* 22, 348–355. <https://doi.org/10.1097/WCO.0b013e32832d9505> [doi].
- Downing Jr, M.J., Antebi, N., Schrimshaw, E.W., 2014. Compulsive use of Internet-based sexually explicit media: adaptation and validation of the Compulsive Internet Use Scale (CIUS). *Addictive Behav.* 10.1016/j.addbeh.2014.03.007; 10.1016/j.addbeh.2014.03.007.
- Ehrin, E., Gawell, L., Högberg, T., de Paulis, T., Ström, P., 1987. Synthesis of [methoxy-³H]- and [methoxy-¹¹C]-labelled raclopride. Specific dopamine-D2 receptor ligands. *J Label Compd Radiopharm* 23, 931–940. <https://doi.org/10.1002/jlcr.2580240808>.
- Feng, Q., Chen, X., Sun, J., Zhou, Y., Sun, Y., Ding, W., Zhang, Y., Zhuang, Z., Xu, J., Du, Y., 2013a. Voxel-level comparison of arterial spin-labeled perfusion magnetic resonance imaging in adolescents with internet gaming addiction. *Behav. Brain Functions* : BBF 9, 33. <https://doi.org/10.1186/1744-9081-9-33> [doi].
- Feng, Q., Chen, X., Sun, J., Zhou, Y., Sun, Y., Ding, W., Zhang, Y., Zhuang, Z., Xu, J., Du, Y., 2013b. Voxel-level comparison of arterial spin-labeled perfusion magnetic resonance imaging in adolescents with internet gaming addiction. *Behav. Brain Functions* : BBF 9, 33. <https://doi.org/10.1186/1744-9081-9-33> [doi].
- Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev. Neurosci.* 12, 652–669. <https://doi.org/10.1038/nrn3119> [doi].
- Gurevich, E.V., Joyce, J.N., 1999. Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. *Neuropsychopharmacology* 20, 60–80 [https://doi.org/S0893-133X\(98\)00066-9](https://doi.org/S0893-133X(98)00066-9) [pii].
- Hald, G.M., Malamuth, N.M., 2008. Self-perceived effects of pornography consumption. *Arch Sex Behav* 37, 614–625. <https://doi.org/10.1007/s10508-007-9212-1>.
- Hietala, J., West, C., Syvalahti, E., Nagren, K., Lehto, P., Sonninen, P., Ruotsalainen, U., 1994. Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. *Psychopharmacology (Berl.)* 116, 285–290.
- Hollander, E., Buchsbaum, M.S., Haznedar, M.M., Berenguer, J., Berlin, H.A., Chaplin, W., Goodman, C.R., LiCalzi, E.M., Newmark, R., Pallanti, S., 2008. FDG-PET study in pathological gamblers. 1. Lithium increases orbitofrontal, dorsolateral and cingulate metabolism. *Neuropsychobiology* 58, 37–47. <https://doi.org/10.1159/000154478> [doi].
- Innis, R.B., Cunningham, V.J., Delforge, J., Fujita, M., Gjedde, A., Gunn, R.N., Holden, J., Houle, S., Huang, S.C., Ichise, M., Iida, H., Ito, H., Kimura, Y., Koepp, R.A., Knudsen, G.M., Knuuti, J., Lammertsma, A.A., Laruelle, M., Logan, J., Maguire, R.P., Mintun, M.A., Morris, E.D., Parsey, R., Price, J.C., Slifstein, M., Sossi, V., Suhara, T., Votaw, J.R., Wong, D.F., Carson, R.E., 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J. Cerebral Blood Flow Metabolism* 27, 1533–1539 <https://doi.org/9600493> [pii].
- Jouts, J., Johansson, J., Niemela, S., Ollikainen, A., Hirvonen, M.M., Piepponen, P., Arponen, E., Alho, H., Voon, V., Rinne, J.O., Hietala, J., Kaasinen, V., 2012. Mesolimbic dopamine release is linked to symptom severity in pathological gambling. *Neuroimage* 60, 1992–1999. <https://doi.org/10.1016/j.neuroimage.2012.02.006> [doi].
- Kafka, M.P., 2010. Hypersexual disorder: a proposed diagnosis for DSM-V. *Arch Sex Behav* 39, 377–400. <https://doi.org/10.1007/s10508-009-9574-7>; 10.1007/s10508-009-9574-7.
- Kafka, M.P., Hennen, J., 2002. A DSM-IV Axis I comorbidity study of males (n = 120) with paraphilias and paraphilia-related disorders. *Sex Abuse* 14, 349–366.
- Kelley, B.J., Duker, A.P., Chiu, P., 2012. Dopamine agonists and pathologic behaviors. *Parkinson's Disease* 2012, 603631. <https://doi.org/10.1155/2012/603631> [doi].
- Kim, S.H., Baik, S.H., Park, C.S., Kim, S.J., Choi, S.W., Kim, S.E., 2011. Reduced striatal dopamine D2 receptors in people with Internet addiction. *Neuroreport* 22, 407–411. <https://doi.org/10.1097/WNR.0b013e3283346e16e>; 10.1097/WNR.0b013e3283346e16e.
- Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. <https://doi.org/10.1038/npp.2009.110>; 10.1038/npp.2009.110.
- Kor, A., Fogel, Y., Reid, R.C., Potenza, M.N., 2013. Should hypersexual disorder be classified as an addiction? *Sex Addict Compulsivity* 20. <https://doi.org/10.1080/10720162.2013.768132> <https://doi.org/10.1080/10720162.2013.768132>; 10.1080/10720162.2013.768132.
- Lee, B., London, E.D., Poldrack, R.A., Farahe, J., Nacca, A., Monterosso, J.R., Mumford, J. A., Bokarius, A.V., Dahlbom, M., Mukherjee, J., Bilder, R.M., Brody, A.L., Mandelkern, M.A., 2009. Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci.* 29, 14734–14740. <https://doi.org/10.1523/JNEUROSCI.3765-09.2009>; 10.1523/JNEUROSCI.3765-09.2009.
- Linnert, J., Peterson, E., Doudet, D.J., Gjedde, A., Moller, A., 2010. Dopamine release in ventral striatum of pathological gamblers losing money. *Acta Psychiatr Scand* 122, 326–333. <https://doi.org/10.1111/j.1600-0447.2010.01591.x>; 10.1111/j.1600-0447.2010.01591.x.
- Luijten, M., Machielsen, M.W., Veltman, D.J., Hester, R., de Haan, L., Franken, I.H., 2014. Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *J. Psychiatry Neurosci.* 39, 149–169. <https://doi.org/10.1503/jpn.130052> [pii].
- Martinez, D., Broft, A., Foltin, R.W., Slifstein, M., Hwang, D.R., Huang, Y., Perez, A., Frankle, W.G., Cooper, T., Kleber, H.D., Fischman, M.W., Laruelle, M., 2004a. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology* 29, 1190–1202. <https://doi.org/10.1038/sj.npp.1300420>.
- Martinez, D., Broft, A., Foltin, R.W., Slifstein, M., Hwang, D.R., Huang, Y., Perez, A., Frankle, W.G., Cooper, T., Kleber, H.D., Fischman, M.W., Laruelle, M., 2004b. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology* 29, 1190–1202. <https://doi.org/10.1038/sj.npp.1300420>.
- Martinez, D., Saccone, P.A., Liu, F., Slifstein, M., Orlowska, D., Grassetti, A., Cook, S., Broft, A., van Heertum, R., Comer, S.D., 2012. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. *Biol. Psychiatry* 71, 192–198. <https://doi.org/10.1016/j.biopsych.2011.08.024>; 10.1016/j.biopsych.2011.08.024.
- Meerkerk, G.J., van den Eijnden, R.J., Vermulst, A.A., Garretsen, H.F., 2009. The Compulsive Internet Use Scale (CIUS): some psychometric properties. *Cyberpsychol Behav.* 12, 1–6. <https://doi.org/10.1089/cpb.2008.0181>; 10.1089/cpb.2008.0181.
- Missale, C., Nash, S.R., Robinson, S.W., Jaber, M., Caron, M.G., 1998. Dopamine receptors: from structure to function. *Physiol. Rev.* 78, 189–225.
- Montgomery, A.J., Lingford-Hughes, A.R., Egerton, A., Nutt, D.J., Grasby, P.M., 2007. The effect of nicotine on striatal dopamine release in man: a [¹¹C]raclopride PET study. *Synapse* 61, 637–645. <https://doi.org/10.1002/syn.20419>.
- Orford, J., 1978. Hypersexuality: implications for a theory of dependence. *Br J Addict Alcohol Other Drugs* 73, 210–299.
- Patton, J.H., Stanford, M.S., Barratt, E.S., 1995. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 51, 768–774.
- Payer, D., Balasubramaniam, G., Boileau, I., 2014. What is the role of the D3 receptor in addiction? A mini review of PET studies with [(11)C]-(+)-PHNO. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 52, 4–8. <https://doi.org/10.1016/j.pnpbp.2013.08.012> [doi].
- Payer, D.E., Guttman, M., Kish, S.J., Tong, J., Strafella, A., Zack, M., Adams, J.R., Rusjan, P., Houle, S., Furukawa, Y., Wilson, A.A., Boileau, I., 2015. [(11)C]-(+)-PHNO PET imaging of dopamine D(2/3) receptors in Parkinson's disease with impulse control disorders. *Movement Disorders* 30, 160–166. <https://doi.org/10.1002/mds.26135> [doi].
- Petry, N.M., 2006. Should the scope of addictive behaviors be broadened to include pathological gambling? *Addiction* 101, 152–160. <https://doi.org/10.1111/j.1360-0443.2006.01593.x>. Suppl.
- Potenza, M.N., 2006. Should addictive disorders include non-substance-related conditions? *Addiction* 101, 142–151. <https://doi.org/10.1111/j.1360-0443.2006.01591.x>. Suppl.
- Reid, R.C., Carpenter, B.N., Hook, J.N., Garos, S., Manning, J.C., Gilliland, R., Cooper, E. B., McKittrick, H., Davtian, M., Fong, T., 2012. Report of findings in a DSM-5 field trial for hypersexual disorder. *J Sex Med* 9, 2868–2877. <https://doi.org/10.1111/j.1743-6109.2012.02936.x>; 10.1111/j.1743-6109.2012.02936.x.
- Roberti, J.W., Storch, E.A., Bravata, E., 2003. Further psychometric support for the Sensation Seeking Scale-Form V. *J Pers Assess* 81, 291–292. https://doi.org/10.1207/S15327752JPA8103_12.
- Ross, M.W., Mansson, S.A., Daneback, K., 2012. Prevalence, severity, and correlates of problematic sexual Internet use in Swedish men and women. *Arch Sex Behav* 41, 459–466. <https://doi.org/10.1007/s10508-011-9762-0>; 10.1007/s10508-011-9762-0.
- Sheehan, D.v, Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59, 22–57. Suppl 2.
- Spreckelmeyer, K.N., Paulzen, M., Raptis, M., Baltus, T., Schaffrath, S., van Waesbergh, J., Zalewski, M.M., Rosch, F., Vernalen, I., Schafer, W.M., Grunder, G., 2011. Opiate-induced dopamine release is modulated by severity of alcohol dependence: an [(18)F]fallypride positron emission tomography study. *Biol.*

- Psychiatry 70, 770–776. <https://doi.org/10.1016/j.biopsych.2011.05.035>, 10.1016/j.biopsych.2011.05.035.
- Steeves, T.D., Miyasaki, J., Zurovski, M., Lang, A.E., Pellecchia, G., van Eimeren, T., Rusjan, P., Houle, S., Strafella, A.P., 2009. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain: a journal of neurology* 132, 1376–1385. <https://doi.org/10.1093/brain/awp054>, 10.1093/brain/awp054.
- Svedin, C.G., Akerman, I., Priebe, G., 2011. Frequent users of pornography. A population based epidemiological study of Swedish male adolescents. *J Adolesc* 34, 779–788. <https://doi.org/10.1016/j.adolescence.2010.04.010>, 10.1016/j.adolescence.2010.04.010.
- Tian, M., Chen, Q., Zhang, Y., Du, F., Hou, H., Chao, F., Zhang, H., 2014a. PET imaging reveals brain functional changes in internet gaming disorder. *Eur. J. Nucl. Med. Mol. Imaging* 41, 1388–1397. <https://doi.org/10.1007/s00259-014-2708-8> [doi].
- Tian, M., Chen, Q., Zhang, Y., Du, F., Hou, H., Chao, F., Zhang, H., 2014b. PET imaging reveals brain functional changes in internet gaming disorder. *Eur. J. Nucl. Med. Mol. Imaging* 41, 1388–1397. <https://doi.org/10.1007/s00259-014-2708-8> [doi].
- Trivedi, M.H., Rush, A.J., Ibrahim, H.M., Carmody, T.J., Biggs, M.M., Suppes, T., Crismon, M.L., Shores-Wilson, K., Toprac, M.G., Dennehy, E.B., Witte, B., Kashner, T. M., 2004. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psych. *Psychol Med* 34, 73–82.
- van Laere, K., Clerinx, K., D'Hondt, E., de Groot, T., Vandenberghe, W., 2010. Combined striatal binding and cerebral influx analysis of dynamic 11C-raclopride PET improves early differentiation between multiple-system atrophy and Parkinson disease. *J Nucl. Med.* 51, 588–595. <https://doi.org/10.2967/jnumed.109.070144> [doi].
- van Rooij, A.J., Schoenmakers, T.M., Vermulst, A.A., van den Eijnden, R.J., van de Mheen, D., 2011. Online video game addiction: identification of addicted adolescent gamers. *Addiction* 106, 205–212. <https://doi.org/10.1111/j.1360-0443.2010.03104.x> [doi].
- Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., Pappas, N., 2001. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry* 158, 2015–2021. <https://doi.org/10.1176/appi.ajp.158.12.2015> [doi].
- Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Hitzemann, R., Chen, A.D., Dewey, S.L., Pappas, N., 1997. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* 386, 830–833. <https://doi.org/10.1038/386830a0>.
- Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Hitzemann, R., Ding, Y.S., Pappas, N., Shea, C., Piscani, K., 1996. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcoholism. Clin. Exp. Res.* 20, 1594–1598.
- Volkow, N.D., Wang, G.J., Ma, Y., Fowler, J.S., Wong, C., Ding, Y.S., Hitzemann, R., Swanson, J.M., Kalivas, P., 2005. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J. Neurosci.* 25, 3932–3939 <https://doi.org/10.1523/JNEUROSCI.3932-05.2005> [pii].
- Wang, G.J., Geliebter, A., Volkow, N.D., Telang, F.W., Logan, J., Jayne, M.C., Galanti, K., Selig, P.A., Han, H., Zhu, W., Wong, C.T., Fowler, J.S., 2011. Enhanced striatal dopamine release during food stimulation in binge eating disorder. *Obesity (Silver Spring)* 19, 1601–1608. <https://doi.org/10.1038/oby.2011.27>, 10.1038/oby.2011.27.
- Wise, R.A., 2006. Role of brain dopamine in food reward and reinforcement. *Philos. Trans R Soc London. Series B, Biol Sci.* 361, 1149–1158. <https://doi.org/10.1098/rstb.2006.1854>.
- Zuckerman, M., Eysenck, S., Eysenck, H.J., 1978. Sensation seeking in England and America: cross-cultural, age, and sex comparisons. *J Consult Clin Psychol* 46, 139–149.