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Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [^{11}C]MADAM

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Abstract

Behavioral addictions, such as pathological gambling (PG) and binge eating disorder (BED), appear to be associated with specific changes in brain dopamine and opioid function, but the role of other neurotransmitter systems is less clear. Given the crucial role of serotonin in a number of psychiatric disorders, we aimed to compare brain serotonergic function among individuals with BED, PG and healthy controls. Seven BED patients, 13 PG patients and 16 healthy controls were scanned with high-resolution positron emission tomography (PET) using the serotonin transporter (SERT) tracer [^{11}C]MADAM. Both region-of-interest and voxel-wise whole brain analyses were performed. Patients with BED showed increased SERT binding in the parieto-occipital cortical regions compared to both PG and healthy controls, with parallel decreases in binding in the nucleus accumbens, inferior temporal gyrus and lateral orbitofrontal cortex. No differences between PG patients and controls were observed. None of the subjects were on SSRI medications at the time of imaging, and there were no differences in the level of depression between PG and BED patients. The results highlight differences in brain SERT binding

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between individuals with BED and PG and provide further evidence of different neurobiological underpinnings in behavioral addictions that are unrelated to the co-existing mood disorder. The results aid in the conceptualization of behavioral addictions by characterizing the underlying serotonin changes and provide a framework for additional studies to examine syndrome-specific pharmaceutical treatments.

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1. Introduction

Behavioral addictions are an emerging concept of phenotypically heterogeneous disorders characterized by repetitive behavioral patterns that persist despite negative consequences (Robbins and Clark, 2015). Pathological gambling (PG) is the most widely studied behavioral addiction. The classification of disorders characterized by repetitive behaviors remains an active area of inquiry. A careful clinical and neurobiological understanding allows us to understand how these behaviors may be related. One of these disorders is binge eating disorder (BED), the most prevalent eating disorder, which has a life-time prevalence of 1.9–3.5% (Hudson et al., 2007; Kessler et al., 2013). The pathological behavior in BED is characterized by repetitive and rapid overeating and a loss of control during eating.

The brain serotonergic system plays a pivotal role in multiple psychiatric disorders, including addictions. For instance, the use of selective serotonin reuptake inhibitors (SSRIs) is not limited to major depression (Olsson and Marcus, 2009) and SSRIs have shown efficacy in anxiety disorders, obsessive-compulsive disorder and bulimia nervosa (Fineberg et al., 2012; Kent et al., 1998; McElroy et al., 2015). The role of SSRIs in the pharmacotherapy of PG is mixed (Bullock and Potenza, 2012), whereas SSRIs have been shown to decrease binge eating behavior among BED patients (Brownley et al., 2016). Serotonin is involved in the neurobiological effects of several drugs of abuse (Kirby et al., 2011) and patients with different drug addictions (stimulants, alcohol, opioids) appear to mainly exhibit reduced brain serotonergic function (Müller and Homberg, 2015). There are several plausible mechanisms by which serotonergic function may be impaired in addictions. The relationship is likely partially mediated by impulsivity, which is itself modulated by 5-HT, and compulsive drug use is associated with abnormal levels of impulsivity (Kirby et al., 2011). Alternatively, the prevalence of mood disorders is 38% and 46% in PG and BED patients, respectively, and anxiety disorders are linked to PG in 37% of cases and in BED in 56–65% of cases (Hudson et al., 2007; Kessler et al., 2013; Lorains et al., 2011). The high susceptibility of PG and BED patients to co-morbid mood and anxiety disorders could indicate specific serotonergic vulnerability in these behaviors.

Earlier studies investigating the serotonergic system in PG or BED are scarce. The only previous functional neuroimaging study that focused on the brain serotonin system in PG found no differences in 5-HT_{1B} receptor availability with [¹¹C]P943 PET between PG patients and controls but demonstrated a positive correlation between tracer binding and gambling symptom severity (Potenza et al., 2013). In addition, an earlier SPECT study with [¹²³I]β-CIT suggested

reduced SERT density in the midbrain among BED patients compared to obese individuals (Kuikka et al., 2001), but a later [¹²³I]ADAM SPECT pilot study reported an opposite effect in six patients with night eating syndrome (Lundgren et al., 2008). PET studies of the brain serotonin system in BED patients have not been reported. Our earlier PET study showed that there are differences in brain dopamine and opioid function between PG and BED patients (Majuri et al., 2017), which suggests that patients with BED have lower μ-opioid receptor availability in widespread cortical and subcortical regions and lower dopamine synthesis capacity in the nucleus accumbens compared to both healthy controls and PG patients.

We therefore sought to determine whether brain serotonin function is impaired in individuals with PG and BED relative to healthy controls. We were specifically interested in differentiating serotonergic function between individuals with PG and BED, similar to our previous findings with dopamine and opioid function. Here, we used a specific SERT tracer [¹¹C]MADAM and high-resolution PET to directly compare serotonin function between the groups of behavioral addicts and a group of healthy volunteers. We hypothesized that BED would be associated with lowered SERT binding in regions related to brain reward processing but would show a different SERT binding pattern compared to PG, thus providing further evidence of the differences between individual behavioral addictions.

2. Experimental procedures

Seven binge eaters, 15 pathological gamblers and 17 healthy volunteers were recruited for the study. Inclusion and exclusion criteria have been described in more detail in our earlier study that included the same population (Majuri et al., 2017). Two pathological gamblers were excluded from the analysis due to excessive intra- and inter-frame head movement during scanning. One healthy volunteer withdrew consent to study participation during scanning and was not included in the analysis. The final sample therefore included 7 BED, 13 PG and 16 healthy subjects. None of the included subjects used serotonergic medications. Demographic data of the study sample is presented in Table 1. Clinical characteristics and symptom severities in BED and PG groups are shown in Table 2.

2.1. Tracer production

[¹¹C]MADAM was synthesized via the ¹¹C-methylation of desmethyl MADAM with [¹¹C]methyl triflate prepared from cyclotron-produced [¹¹C]methane using a previously described method (Halldin et al., 2005), with minor modifications. Radiochemical purity exceeded 95%

Table 1 Main demographic data and questionnaire data. Values are mean (SD) or n.

	HC	PG	BED	P-value ^a
<i>n</i>	16	13	7	
Age (years)	42.4 (10.8)	43.0 (12.7)	49.4 (5.1)	0.336
Sex (m/f)	7/9	6/7	0/7	0.088
BMI (kg/m ²)	25.0 (2.1)	25.2 (4.0)	30.9 (6.6)	0.006
Smoking (y/n)	7/9	11/2	2/5	0.024
BDI	2.69 (3.1)	14.5 (8.0)	15.4 (9.6)	<0.001
AUDIT	5.4 (3.4)	5.2 (3.4)	3.3 (1.1)	0.302
Injected dose of [¹¹ C]MADAM (MBq)	499 (16)	485 (24)	501 (13)	0.081
Injected mass of [¹¹ C]MADAM (ng)	444 (257)	357 (88)	315 (114)	0.257

BMI = body mass index, BDI = Beck Depression Inventory, AUDIT = Alcohol Use Disorders Identification Test.

^aOne-way ANOVA or Fisher's exact test.

Table 2 Differences between studied groups in gambling and eating. Values are mean (SD).

Behavior	Item	HC	PG	BED	P-value ^a
Gambling	PG DSM-IV	0.1 (0.3)	7.3 (1.4)	0 (0)	<0.001
	SOGS	0.1 (0.3)	13.1 (2.3)	0.4 (0.5)	<0.001
	Duration of problem gambling (years)	0 (0)	10.2 (6.6)	0 (0)	<0.001
	Gambling per week (€)	2.2 (3.1)	137 (118)	2.5 (4.3)	<0.001
	Gambling per week (hours)	0.2 (0.3)	9.9 (7.0)	0.5 (1.1)	<0.001
	Gambling debt (€)	0 (0)	14,700 (14,000)	0 (0)	<0.001
Eating	Binge Eating Scale	2.2 (2.1)	4.9 (4.5)	30.9 (4.6)	<0.001
	Yale food addiction scale	5.3 (3.5)	8.9 (9.8)	42.3 (6.5)	<0.001
	DEBQ emotional	20.9 (5.0)	20.5 (8.6)	50.0 (8.3)	<0.001
	DEBQ external	23.7 (5.5)	25.9 (7.5)	37.5 (6.3)	<0.001
	DEBQ restrained	23.9 (6.0)	20.2 (10.7)	35.3 (3.4)	0.001
	Duration of problem eating (yrs)	0 (0)	0 (0)	18.1 (14.9)	<0.001

PG DSM-IV = DSM-IV diagnostic criteria for pathological gambling, SOGS = South Oaks Gambling Screen, DEBQ = The Dutch Eating Behavior Questionnaire.

^aOne-way ANOVA.

in all production runs and the average specific activity was 395 GBq/μmol (SD 130) at the time of injection.

2.2. Scanning protocol

Subjects were scanned using a High Resolution Research Tomograph PET scanner (HRRT, Siemens Medical Solutions, Knoxville, TN, USA) in 3D mode with scatter correction. A transmission scan was performed before dynamic scans for attenuation correction and was carried out with a ¹³⁷Cs rotating point source. The dynamic scan was divided into 19 frames (3 × 1 min, 4 × 3 min, 10 × 6 min and 2 × 7.5 min), and the total scanning time was 90 min. Head movements during scanning were recorded with a stereotaxic infrared camera (Polaris Vicra, Northern Digital, Waterloo, Canada) and reduced with an individually shaped thermoplastic mask. Three PG patients had a Velcro strap instead of a thermoplastic mask because they did not tolerate the latter.

2.3. Image preprocessing

Image preprocessing was performed via SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) on Matlab R2012a (MathWorks, Natick, MA, USA), as described previously (Majuri et al., 2017). Briefly, between-frame motion in the PET images was corrected, and PET images were coregistered to T1-weighted MRI images using a mutual information algorithm. Individual multiple-acquisition frame reconstructions were made for four PG patients and one control subject to compensate for excessive in-frame head motion (Johansson et al., 2016). Regions of interest (ROIs) were created by running the structural MRI parcellation with FreeSurfer software (version 5.3.0, <http://surfer.nmr.mgh.harvard.edu/>) (Desikan et al., 2006; Fischl et al., 2002). ROIs included in primary group comparisons were the putamen, nucleus caudatus, nucleus accumbens, globus pallidus, thalamus, amygdala, hippocampus and cortical gray matter regions. [¹¹C]MADAM non-displaceable binding potentials (*BP_{ND}*) were estimated with a simplified reference tissue model using the cerebellar cortex as a reference region (Gunn et al., 1997). For the voxel-wise whole brain analysis, parametric images were created in the subjects' native space and then warped

to the Montreal Neurological Institute standard space (MNI152) using the structural information of the MRI images by applying the DARTEL normalization algorithm (Ashburner, 2007). An analysis that covered the entire cerebral gray matter (all brain areas in the TD Lobes library except cerebellar brain regions) was created with the TD-ICBM Human Atlas in the WFU Pick Atlas (Lancaster et al., 2000; Maldjian et al., 2003).

2.4. Statistical analyses

Statistical analyses were run on SPSS (IBM SPSS Statistics, version 22, Armonk, NY, USA). Group differences were investigated with Fisher's exact test or one-way ANOVA with Bonferroni correction for *post hoc* tests. Within-group correlation analyses between tracer binding and questionnaire and demographic data were performed with the Spearman rank order test. Similar voxel-wise analyses were performed using a general linear model with SPM8. The multiple comparisons problem caused by multiple investigated brain regions was addressed using two different approaches: the threshold for statistically significant ROI-based group comparisons was set at 0.01, and the cluster-level family-wise error (FWE) correction was applied in SPM analyses (corrected *p*-value less than 0.05). Statistically significant clusters were visualized on the brain surface via BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (Xia et al., 2013).

3. Results

BED patients showed increased [^{11}C]MADAM binding in the bilateral superior and inferior parietal cortices and the bilateral lateral occipital cortex when compared to healthy controls and PG patients (Table 3). The greatest increases were seen in the superior parietal cortex, where BED patients had 122% higher tracer binding when compared to controls and 108% higher binding when compared to PG patients ($p < 0.001$). When the left and right hemispheres were analyzed separately, the results remained the same in both the right and left inferior parietal cortex. In the lateral occipital and superior parietal cortices, only the right hemisphere showed statistically significant differences (left lateral occipital cortex: $p = 0.088$, right: $p < 0.001$; left superior parietal cortex: $p = 0.061$, right: $p < 0.001$).

In contrast, significant decreases in [^{11}C]MADAM binding were observed in the nucleus accumbens, inferior temporal gyrus and lateral orbitofrontal cortex in the BED group when compared to healthy controls (Table 3). [^{11}C]MADAM BP_{ND} was 28% lower in the BED group than in healthy controls in the nucleus accumbens ($p = 0.006$), but the difference between BED and PG was not statistically significant. When hemispheres were analyzed separately, the effects in left and right nucleus accumbens were non-significant but remained significant in the left and right inferior temporal gyrus and the left and right lateral orbitofrontal cortex.

Sub-group analyses were performed first by excluding all male subjects from the analysis and then by excluding all smokers (Figure 1). Excluding males did not change the primary results: in the nucleus accumbens, the corrected model remained statistically significant ($p = 0.004$; Bonferroni post hoc $p = 0.018$), and the group difference between PG and BED patients emerged as significant ($p = 0.005$). When smokers were excluded, the results remained the same in the areas that showed increased BP_{ND} values in the primary analysis but became non-significant in the nucleus accumbens ($p = 0.13$). Correlation analyses with tracer

Table 3 Group differences in ANOVA. HC = Healthy controls, PG = Pathological gambling, BED = Binge eating disorder. Binding values are BP_{ND} (means and SD).

Region	HC	PG	BED	F-value One-way ANOVA	P-value One-way ANOVA	P-value ^a C vs PG	P-value ^a C vs BED	P-value ^a PG vs BED
Superior parietal cortex	0.222 (0.090)	0.237 (0.072)	0.492 (0.203)	14.99	<0.001	1.00	<0.001	<0.001
Inferior parietal cortex	0.298 (0.082)	0.318 (0.084)	0.477 (0.071)	12.86	<0.001	1.00	<0.001	0.001
Lateral occipital cortex	0.231 (0.060)	0.216 (0.080)	0.372 (0.090)	11.51	<0.001	1.00	0.001	<0.001
Inferior temporal gyrus	0.286 (0.055)	0.263 (0.039)	0.196 (0.045)	8.643	0.001	0.591	0.001	0.017
Lateral orbitofrontal cortex	0.410 (0.083)	0.395 (0.091)	0.280 (0.067)	6.245	0.005	1.00	0.005	0.018
Nucleus accumbens	1.656 (0.394)	1.500 (0.225)	1.193 (0.141)	5.642	0.008	0.536	0.006	0.117

^aBonferroni corrected post hoc tests.

Figure 1 [^{11}C]MADAM BP_{ND} values in the region-of-interest analysis. Between-group differences are presented above each panel indicating the significance level in Bonferroni corrected post hoc tests. NS = non-significant, * = $p < 0.01$, ** = $p < 0.001$. A: superior parietal cortex, all subjects. B: superior parietal cortex, women only. C: superior parietal cortex, non-smokers only. D: nucleus accumbens, all subjects. E: nucleus accumbens, women only. F: nucleus accumbens, non-smokers only.

Figure 2 Group differences in voxel-wise analyses. The red-yellow clusters indicate brain areas where patients with binge eating disorder had significantly higher [^{11}C]MADAM uptake when compared to pathological gamblers (Family-wise error corrected $p < 0.05$). Large clusters were seen in the right occipital cortex and the left parietal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

binding and symptom severity, including symptom duration, body mass index (BMI), questionnaire data and depression scores, were non-significant in the BED group. Lastly, the group differences were examined applying an analysis of covariance using BDI and BMI as covariates. The results remained significant in the parietal and lateral occipital cortices.

Finally, the results concerning increased binding were confirmed in the voxel-wise analysis. Binge eaters had greater binding in the right occipital cortex (cluster size 44.4 cm^3 , peak voxel at 18, -51, 4 mm, $t_{\max} = 5.68$, $p_{FWE} =$

0.001) and in the left parietal cortex (cluster size 31.7 cm^3 , peak voxel at -51, -57, 19 mm, $t_{\max} = 5.36$, $p_{FWE} = 0.009$) compared to PG patients (Figure 2). There were no areas where BED patients showed lower tracer binding in the voxel-based analysis compared to PG patients or healthy controls, and there were no differences between the PG and HC groups.

4. Discussion

The results of this study indicate that central SERT binding in PG patients does not differ from healthy controls, but there is regionally selective SERT up- and downregulation in individuals with BED. Although BED patients had more depressive symptoms compared to healthy volunteers, the depression scores were the same between BED and PG subjects, and there was no correlation between SERT binding and depression. Therefore, these alterations in SERT function are likely not mood-related but rather demonstrate syndrome-specific differences in serotonergic function between two phenotypically different behavioral addictions.

We have previously reported reductions in opioid and dopamine neurotransmitter systems in this same BED patient cohort compared to PG and healthy controls (Majuri et al., 2017). Using [^{11}C]carfentanil PET, we showed decreased μ -opioid receptor availability in multiple cortical and subcortical regions, including the nucleus accumbens and the lateral orbitofrontal cortex, when compared to healthy controls and PG patients. We additionally reported that BED patients have decreased dopamine synthesis capacity in the nucleus accumbens with [^{18}F]fluorodopa PET whereas differences between PG patients and controls were minimal. Here, we report large increases in [^{11}C]MADAM binding in the lateral occipital cortex and the parietal cortex in BED patients with decreased binding in structures related to the brain reward system, including the nucleus accumbens, the lateral orbitofrontal cortex and the

inferior temporal gyrus. Increased SERT binding was consistently seen with ROI- and voxel-based analyses, and the magnitude of the relative difference between groups was 50–122%, depending on the region. Decreased binding was detected with the ROI-analysis but not the voxel-based analysis, which suggests a weaker effect size and limited power, given the small number of BED patients. Current sample sizes were in any case sufficient to demonstrate clear differences in SERT binding between the behavioral addictions. The regional distribution of the findings is of particular interest as the lateral occipital cortex is important in the analysis of visual and haptic representations of objects (Erdogan et al., 2016) whereas the parietal cortex is involved in attentional processing and integrates sensory information from visual and auditory cortices to guide goal-directed actions (Rohe and Noppeney, 2016). We speculate that these regions may contribute to the interpretation of sensory food cues and sensations related to eating in BED, but this theory needs verification from additional studies. In contrast, our ROI findings emphasize lower SERT levels in regions such as the nucleus accumbens and lateral orbito-frontal cortex in BED; these neural regions have also been implicated in cognitive processes associated with BED and serotonin function, including delay discounting, impaired goal-directed control, and the processing of value to guide flexible behavior such as reversal learning (Banca et al., 2016; Mole et al., 2015; Voon, 2015; Voon and Dalley, 2016).

Our findings underline neurobiological differences between substance use disorders and behavioral addictions. 3,4-methylenedioxymethamphetamine (MDMA) has been previously linked to reduced SERT availability in the occipital and parietal cortices with no alterations in basal ganglia (Roberts et al., 2016). Other studies have replicated widespread decreases in SERT availability in MDMA addiction (Erritzoe et al., 2011; McCann et al., 2005). Notably, MDMA binds to the serotonin transporter and inhibits uptake. Whether these findings represent a downregulation in serotonin transporter density secondary to MDMA administration or a decrease in serotonergic terminal density remains to be established (Vegting et al., 2016). Furthermore, in post-mortem studies of human methamphetamine users, SERT availability has been reported to be decreased in orbitofrontal and occipital cortices (Kish et al., 2009). Methamphetamine has been shown to be neurotoxic to serotonergic neurons (Gross et al., 2011). The findings in alcohol dependence are somewhat mixed. Extensive losses in SERT density were observed in a PET study with [^{11}C](+) McN5652 (Szabo et al., 2004), whereas another PET study with [^{11}C]DASB found no differences in SERT availability between controls and alcohol dependent patients (Brown et al., 2007). Our results thus emphasize the findings in behavioral addictions without the confounder of serotonergic toxicity from the drug of abuse. Our results contrast with previous studies in drug and alcohol-dependent patients first by showing that SERT binding in PG is normal and second by showing increased parieto-occipital SERT in individuals with BED. These results thus suggest that behavioral and drug addictions may differ in terms of SERT function, although both are associated with high levels of co-morbid depression and anxiety.

In the interpretation of these findings, it should be noted that our BED group consisted only of seven subjects, and

therefore these results should be considered as preliminary and confirmed in future studies with a larger cohort. However, the effect size for the BP_{ND} difference between BED and healthy controls was large in the superior parietal cortex (Cohen's $d = 1.72$, effect size $r = 0.65$) and the nucleus accumbens (Cohen's $d = 1.56$, effect size $r = 0.62$). Although the binding potentials in cortical brain regions were relatively low compared to subcortical ROIs, previous test-retest data have indicated that [^{11}C]MADAM BP_{ND} reproducibility in cortical brain regions is good (Lundberg et al., 2006). Finally, the present group-differences were not explained by differences in age, BMI, sex or smoking. Only smoking slightly affected to the tracer binding, and after all smokers were excluded from the analyses, significant group differences could still be identified in the superior and inferior parietal cortices and the lateral occipital cortex. Previous studies have demonstrated mixed results between the correlation between BMI and SERT availability. One [^{123}I]FP-CIT SPECT study found positive correlation in thalamus (Hesse et al., 2014) whereas another SPECT study using [^{123}I]nor- β -CIT found no correlation (Koskela et al., 2008). On the other hand, Erritzoe et al. reported negative correlation between SERT availability and BMI in subcortical regions, but also in cortical regions including parietal cortex, using [^{11}C]DASB (Erritzoe et al., 2010). Our BED patients showed elevated BP_{ND} values in the parietal and occipital cortices, indicating that the results in cortical regions were not driven by group differences in BMI.

In summary, together with our previous findings using opioid and dopamine tracers, this study reveals that BED is associated with abnormalities in multiple neurotransmitter systems, including the serotonergic system. Whether these are risk factors for binge eating behaviors or represent compensatory effects remains to be established. The demonstrated differences between behavioral addictions and between behavioral and substance addictions are important for the general conceptualization of behavioral addictions in the field of addiction medicine.

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Contributors

Ju.J., Ja.J., V.V., R.P., H.A., E.A. and V.K. designed the study and wrote the protocol. J.M., Ju.J. and V.K. were responsible of the data collection. J.M., Ju.J., Ja.J. and V.K. undertook the statistical analysis, and J.M. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr Joutsa has received travel grants from Abbvie and Orion, and a research grant from the Orion Research Foundation. All other authors declare no conflicts of interest.

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