European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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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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Received 9 July 2017; received in revised form 11 September 2017; accepted 25 September 2017

KEYWORDS
[^{11}C]MADAM;
Binge eating;
Pathological gambling;
Positron emission tomography;
Serotonin;
Serotonin transporter

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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http://dx.doi.org/10.1016/j.euroneuro.2017.09.007
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Please cite this article as: Majuri, J., et al., Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [^{11}C]MADAM. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.09.007

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 (Olfson 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 [^{11}C]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 [^{123}I]β-CIT suggested reduced SERT density in the midbrain among BED patients compared to obese individuals (Kuikka et al., 2001), but a later [^{123}I]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 [^{11}C]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

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

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